DBCG 07-READ

A randomized phase III trial comparing six cycles of docetaxel and cyclophosphamide (DC) to three cycles of epirubicin and cyclophosphamide followed by three cycles of docetaxel (EC-D) in patients with early BC

DBCG Danish Breast Cancer Cooperative Group

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- Sponsored by the DBCG
- Launced in 2008
- Included 2012 patients
- 5 year results at SABCS 2016

San Antonio Breast Cancer Symposium - December 6-10, 2016

DBCG 07-READ

A randomized phase III trial comparing six cycles of docetaxel and cyclophosphamide (DC) to three cycles of epirubicin and cyclophosphamide followed by three cycles of docetaxel (EC-D) in patients with early breast cancer

Bent Eilertsen, Malgorzata K. Tuxen, Erik H. Jakobsen, Maj-Britt Jensen, Ann S. Knoop, Inger Højris, Marianne Ewertz, Eva Balslev, Peter Michael Vestlev, Julia Kenholm, Dorte L. Nielsen, Troels Bechmann, Michael Andersson, Søren Cold, Hanne M. Nielsen, Else Maae, Dorte Carlsen, Henning Mouridsen

for the **Danish Breast Cancer Cooperative Group (DBCG)**

READ Trial; Aim

- The aim of the present trial is to test the hypothesis from the previous DBCG 89D trial of CMF versus CEF that patients withTOP2A normal tumors will derive no benefit from anthracycline

Knoop AS, et al. J Clin Oncol 2005; 23: 7483
Di Leo A, et al. Lancet Oncol 2011; 12: 1134

EUROPEAN JOURNAL OF CANCER 43 (2007) 877–884

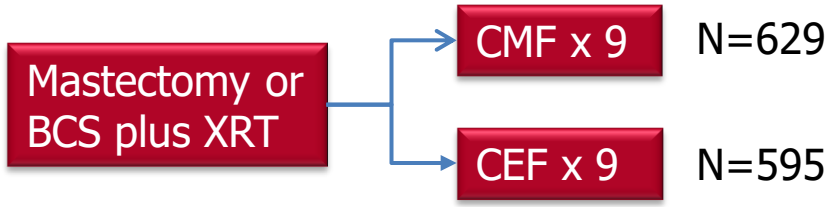
Improved outcome for substituting methotrexate with epirubicin: Results from a randomised comparison of CMF versus CEF in patients with primary breast cancer

Bent Ejlertsen, Henning T. Mouridsen, Maj-Britt Jensen, Jørn Andersen, Søren Cold, Per Edlund, Marianne Ewertz, Brita B.Jensen, Claus Kamby, Bo Nordenskjold, Jonas Bergh.

DBCG 89D Trial Schema

Patient selection

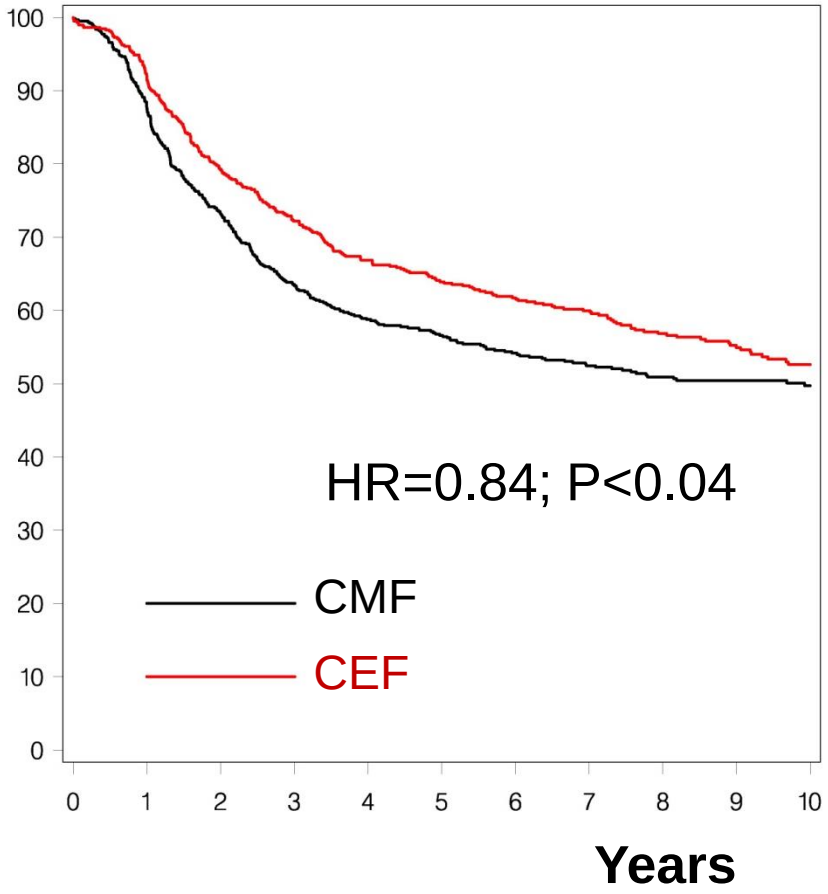
A. Premenopausal, high risk, node negative
B. Premenopausal, node positive, ER-/PgR negative or unknown
C. Postmenopausal, node positive, ER-/PgR negative



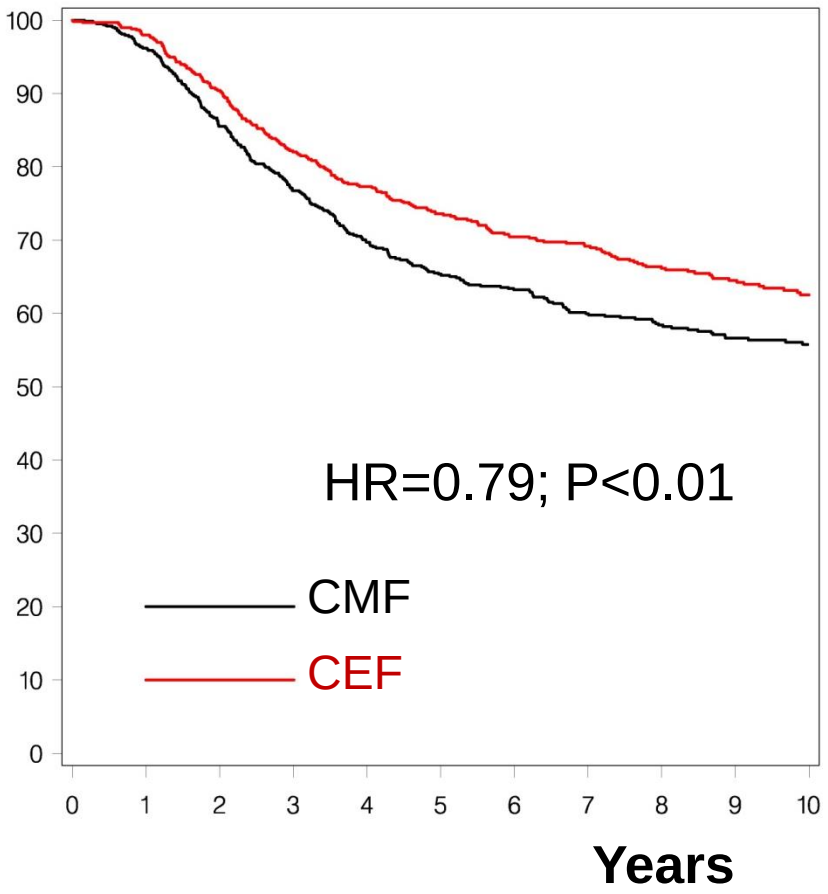
C: cyclophosphamide 600 mg/m^2
F: 5-fluorouracil 600 mg/m^2
M: methotrexate 40 mg/m^2
E: epirubicin 60 mg/m^2

DBCG 89D Trial Results

Disease-Free Survival (%)



Overall Survival (%)



Anthracyclines

- Anthracyclines are topoisomerase II inhibitors
  - The mode of action is identical for doxorubicin and epirubicin
- In early breast cancer anthracycline-based chemotherapy provides an absolute 3% benefit in survival at 10 year compared to CMF
- Average benefits observed in randomized trials or meta-analyses may be explained by a small number of patients having a much larger benefit

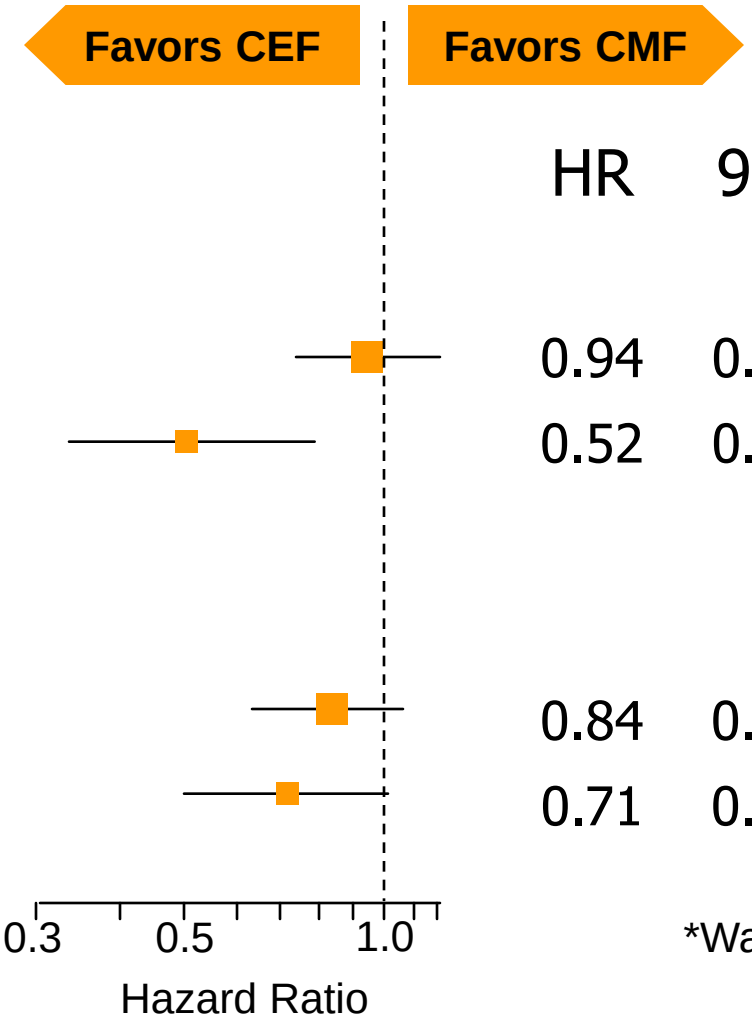
VOLUME 23 · NUMBER 30 · OCTOBER 20 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Retrospective Analysis of Topoisomerase IIa Amplifications and Deletions As Predictive Markers in Primary Breast Cancer Patients Randomly Assigned to Cyclophosphamide, Methotrexate, and Fluorouracil or Cyclophosphamide, Epirubicin, and Fluorouracil: Danish Breast Cancer Cooperative Group

Ann S. Knoop, Helle Knudsen, Eva Balslev, Birgitte B. Rasmussen, Jens Overgaard, Kirsten V. Nielsen, Andreas Schonau, Katrín Gunnarsdóttir, Karen E. Olsen, Henning Mouridsen, and Bent Ejlertsen

Disease-Free Survival



	N	HR	95% CI	P*
TOP2A				
Normal	589	0.94	0.73-1.20	.0003
Abnormal	178	0.52	0.34-0.79	
HER2				
Negative	523	0.84	0.64-1.09	n.s.
Positive	244	0.71	0.50-1.01	

*Wald test of interaction

Knoop et al. J Clin Oncol 2005
Nielsen et al. Acta Oncol 2008
Ejlertsen et al. J Clin Oncol 2010

Lancet Oncol 2011; 12: 1134–42

Published Online
September 13, 2011
DOI:10.1016/S1470-2045(11)70231-5

HER2 and *TOP2A* as predictive markers for anthracycline-containing chemotherapy regimens as adjuvant treatment of breast cancer: a meta-analysis of individual patient data

Angelo Di Leo, Christine Desmedt, John M S Bartlett, Fanny Piette, Bent Ejlertsen, Kathleen I Pritchard, Denis Larsimont, Christopher Poole, Jorma Isola, Helena Earl, Henning Mouridsen, Frances P O'Malley, Fatima Cardoso, Minna Tanner, Alison Munro, Chris J Twelves, Christos Sotiriou, Lois Shepherd, David Cameron, Martine J Piccart, Marc Buyse, for the HER2/TOP2A Meta-analysis Study Group

	DFS HR (95% CI)	$P_{Interaction}$	**OS** HR (95% CI)	$P_{interaction}$
TOP2A (normal or altered)	0.64 (0.50-0.81)	0.018	0.67 (0.52-0.86)	0,045
HER2 (normal or amplified)	0.71 (0.58-0.86)	0.0486	0.73 (0.58-0.89)	0.072

READ trial design

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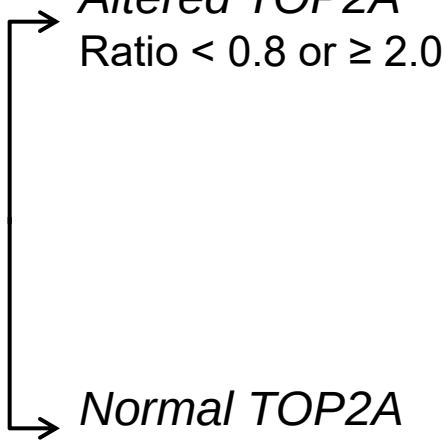
Selection Criteria

Invasive breast cancer
Comorbidity index < 3
High risk

1. Node positive
2. High risk node neg.
   - Young age
   - ER negative
   - HER2+
   - T size
   - High grade



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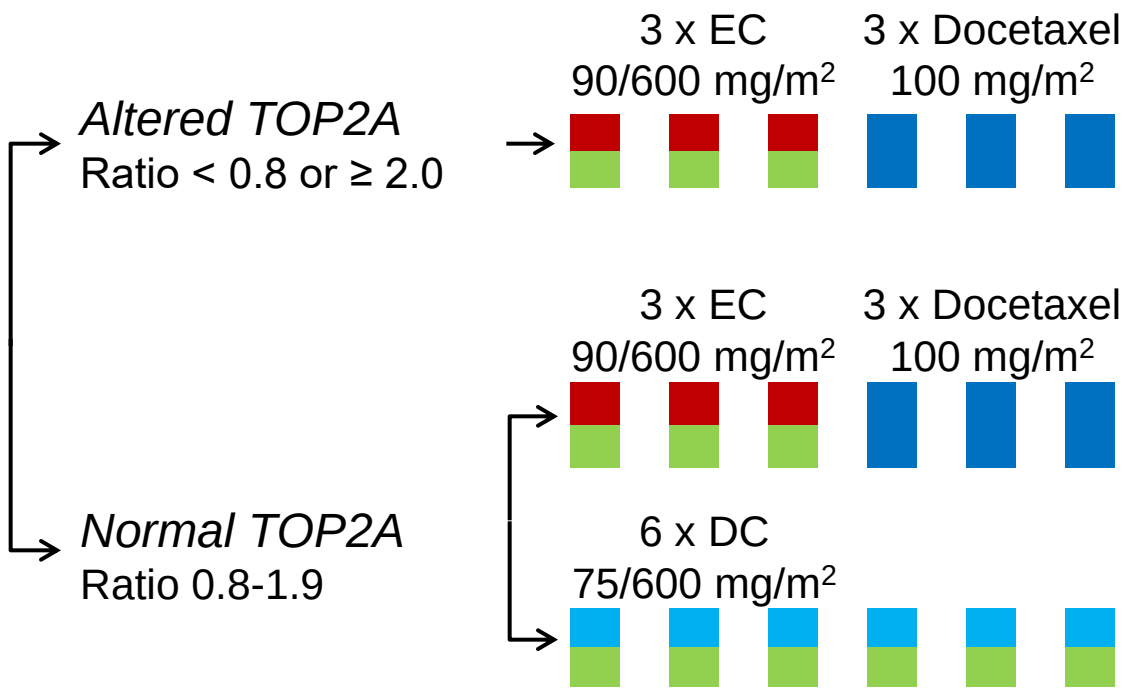

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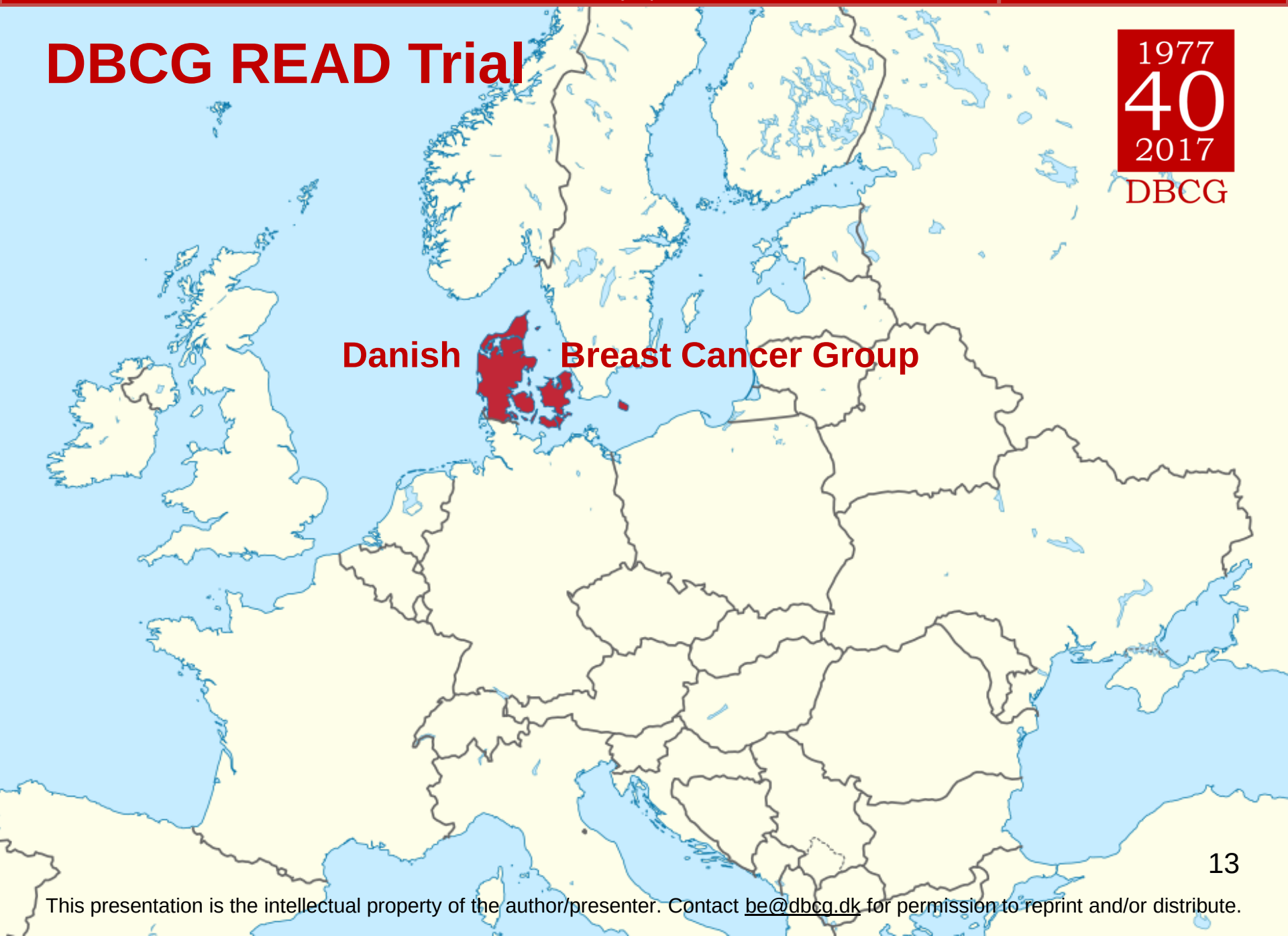
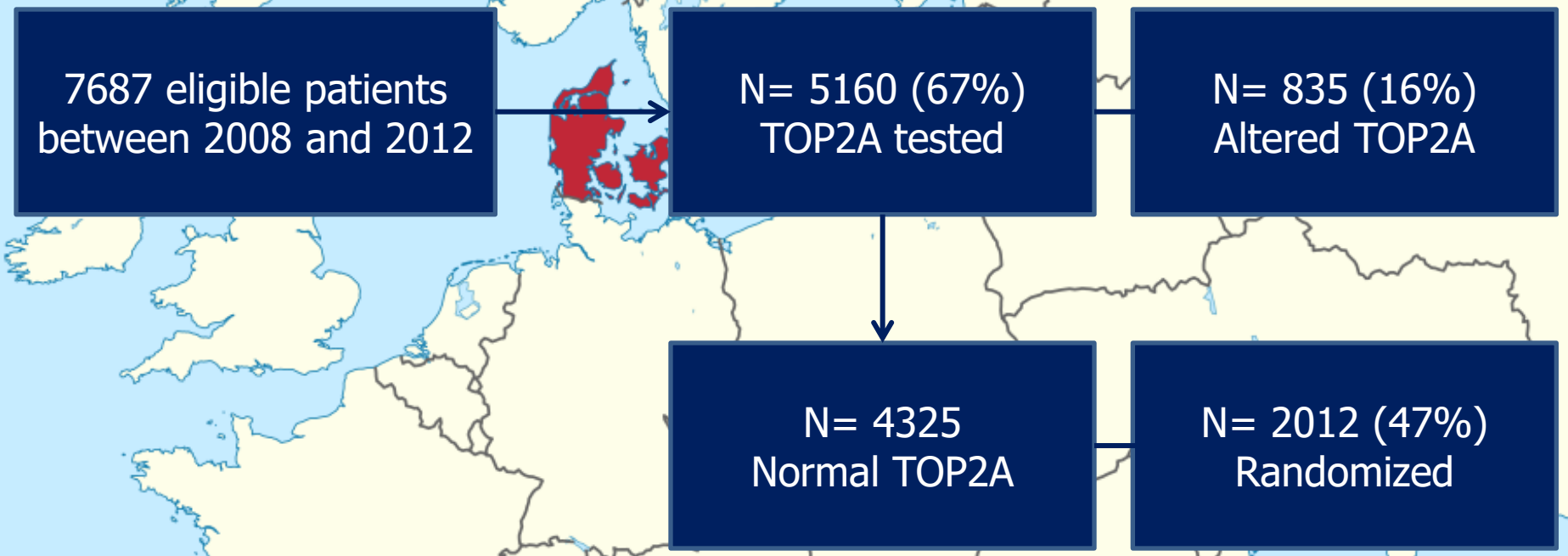
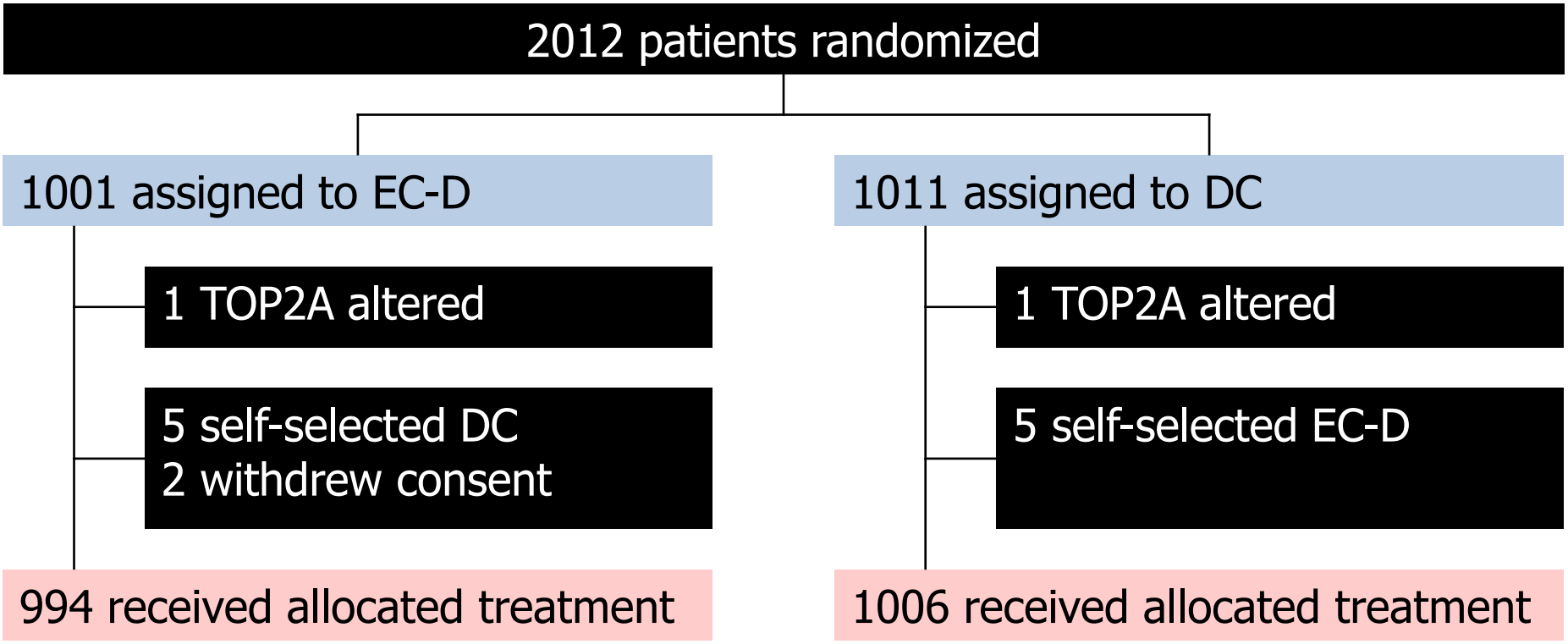


DBCG READ Trial



Trial profile



Statistical plan

- The primary analysis concerns invasive DFS for ITT population
- DFS defined as time to recurrence of invasive BC (local, regional, or distant), any new invasive cancer, or death from any cause
- Secondary endpoints defined as OS, and patient reported safety
- All randomized patients with informed consent included in the ITT population
- Patients who initiated randomized treatment and provided at least one safety assessment included in the safety analysis
- The 1st analysis conducted after 5 years follow-up

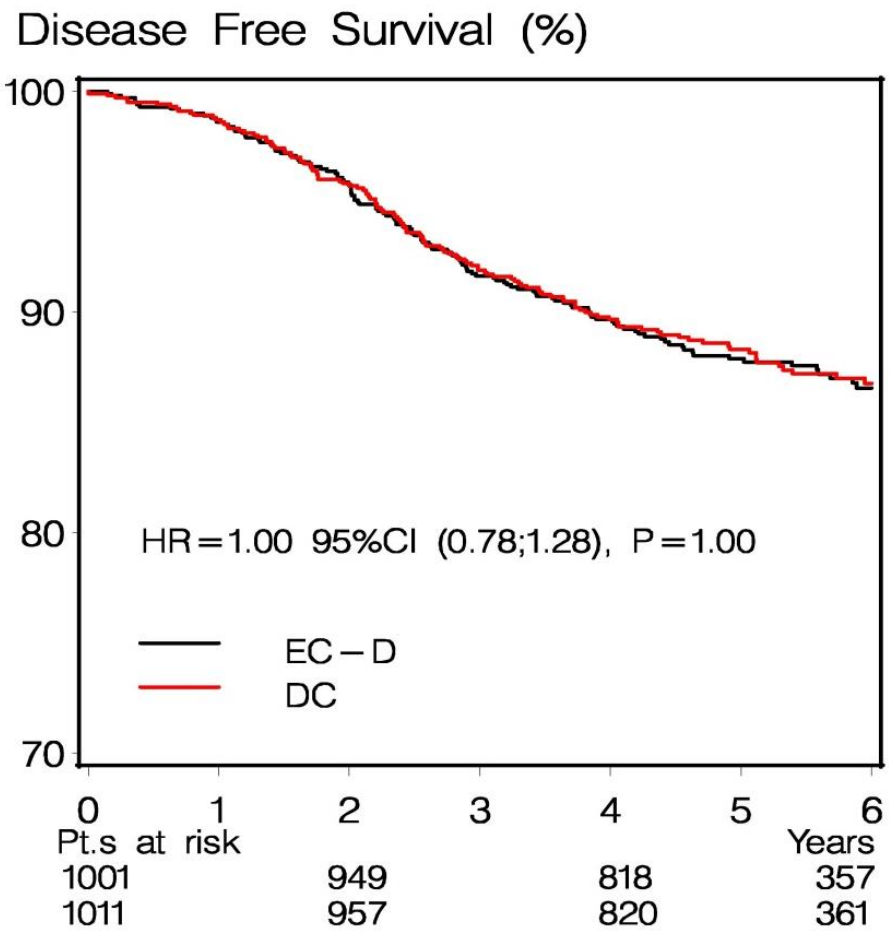
Patient characteristics

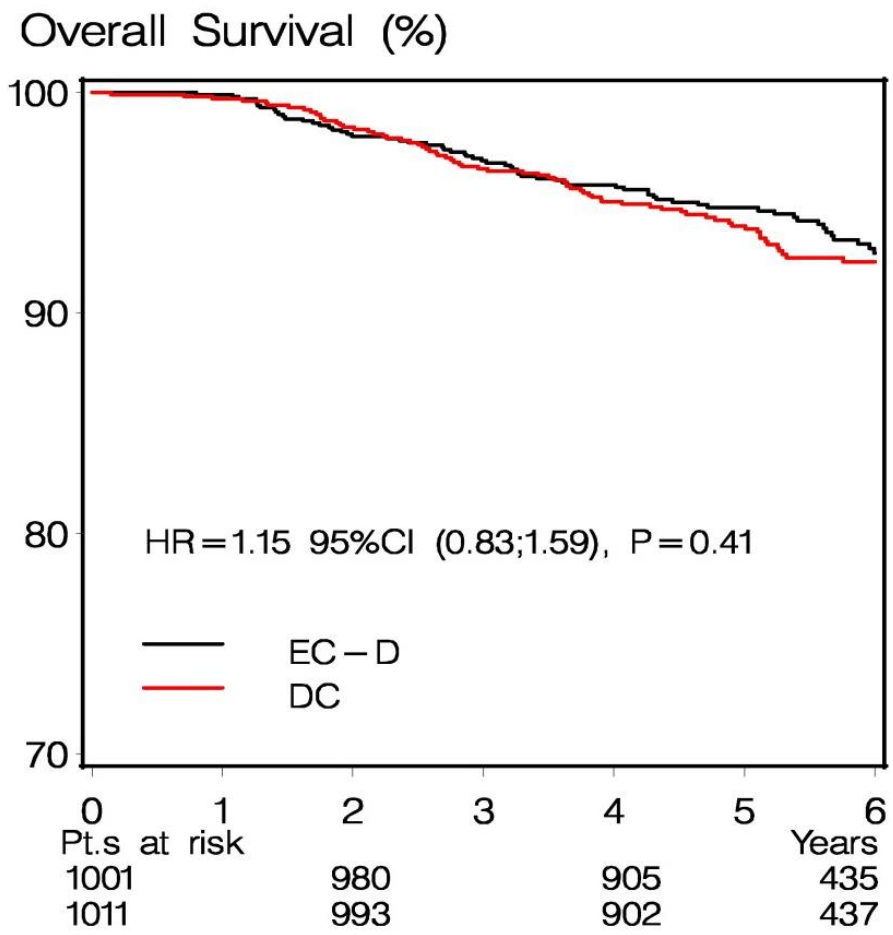
n(%)		EC-D (N=1001)	DC (N=1011)
Age at diagnosis	< 45	205 (20)	199 (20)
	45 – 49	199 (20)	204 (20)
	50 -54	230 (23)	277 (27)
	55-59	265 (26)	237 (23)
	60-74	102 (10)	94 (9)
Menopausal status	Premenopausal	508 (51)	544 (64)
	Postmenopausal	493 (49)	467 (46)
Co-morbidity	Absent (0)	900 (90)	926 (92)
	Present (1-2)	101 (10)	85 (8)

Tumor characteristics

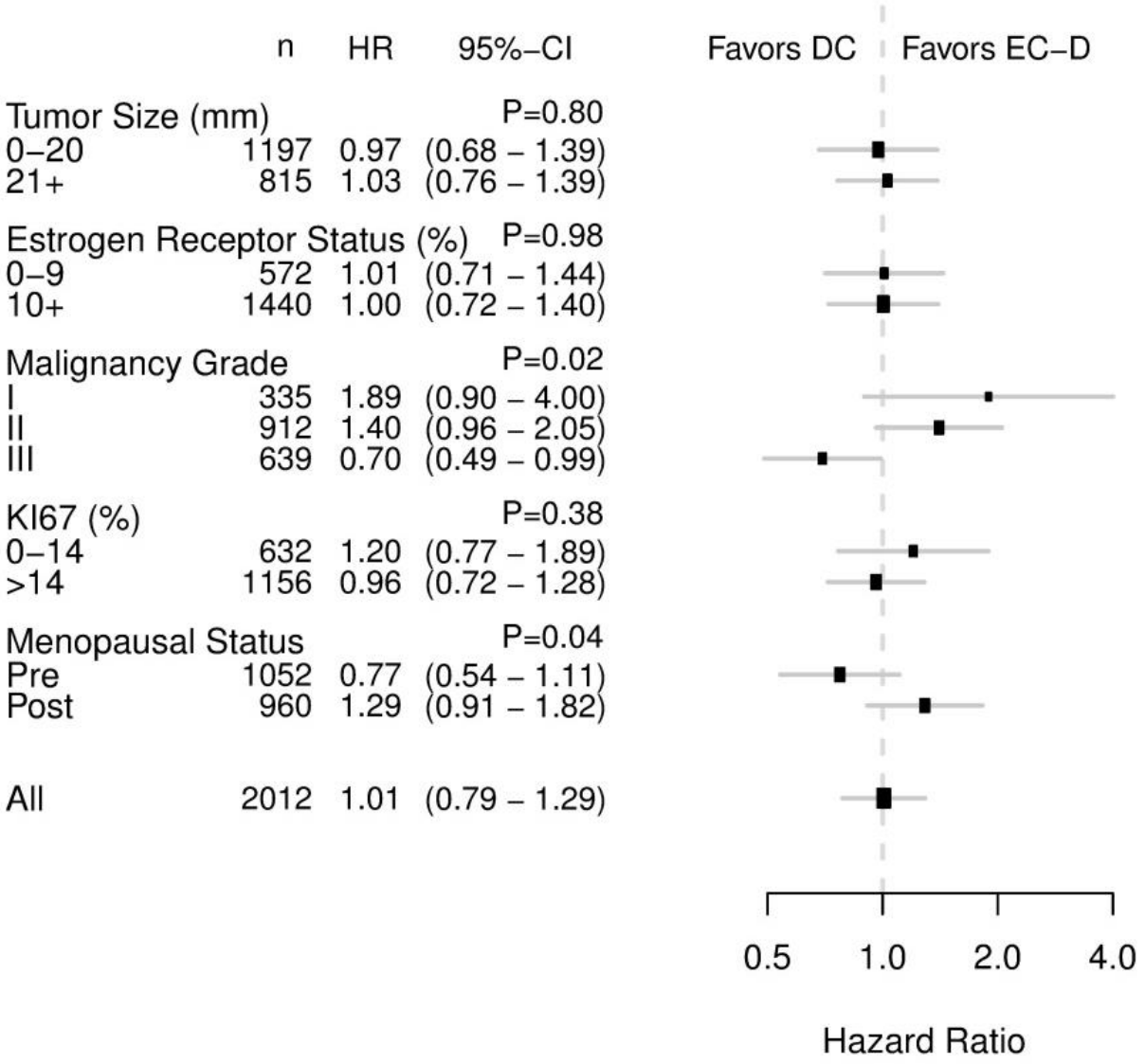
n(%)		EC-D (N=1001)	DC (N=1011)
Tumor size	0 - 10	131 (13)	127 (13)
	11 - 20	487 (49)	452 (45)
	>20	383 (38)	432 (43)
Node negative		448 (45)	467 (46)
Malignancy grade (only ductal/lobular)	Grade 1	159 (16)	176 (17)
	Grade 2	453 (45)	459 (45)
	Grade 3	328 (33)	311 (31)
	Other types	56 (6)	53 (5)
ER positive (≥10%)		702 (70)	738 (73)
HER2 positive (IHC 3+ / FISH ≥ 2.0)		113 (11)	109 (11)
Ki67 high (> 14%, N=1788)		588 (66)	568 (64)

Results; DFS and OS





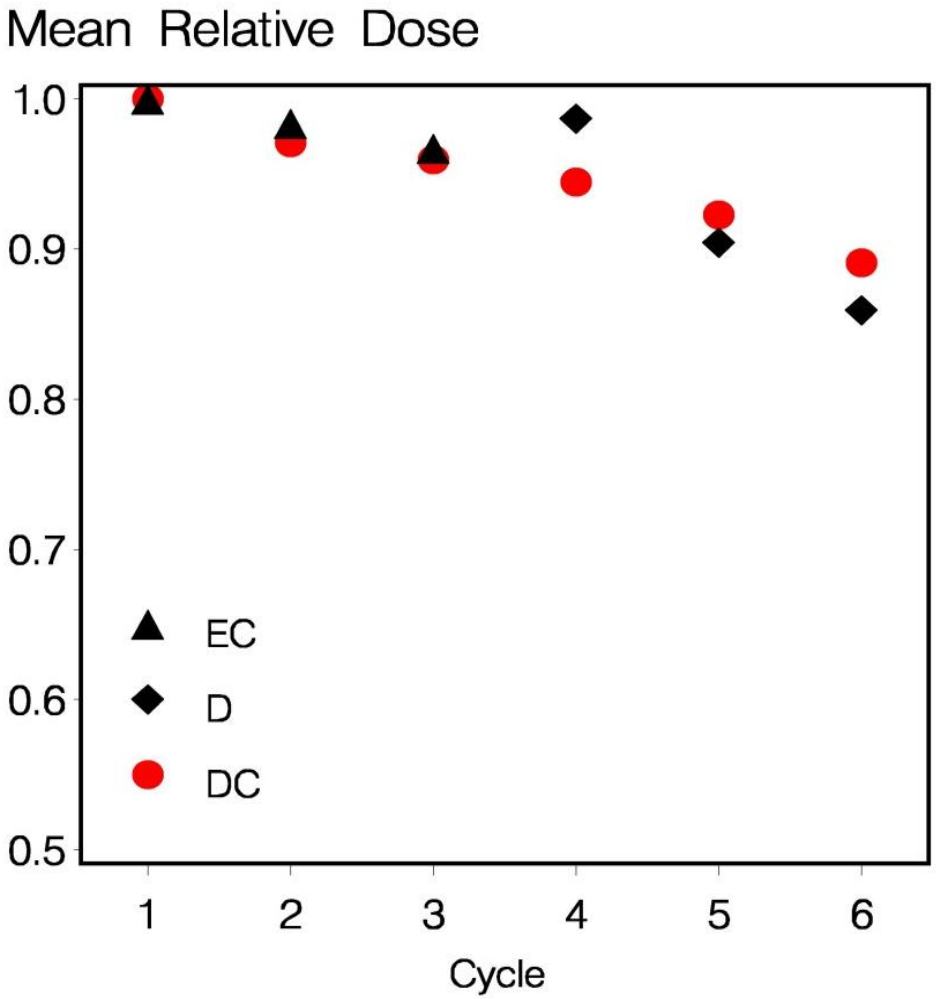
Results; DFS in subgroups



PRO's; adverse events

n(%)	EC-D (N=988)		DC (N=1004)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Mucositis*	848 (86)	25 (3)	800 (80)	11 (1)
Myalgia/arthralgia*	942 (96)	427 (43)	956 (95)	331 (33)
Peripheral neuropathy[t]	722 (73)	121 (12)	683 (68)	85 (8)
Rash/skin disorders	630 (64)	25 (3)	625 (62)	14 (1)
Nails changes	716 (73)	- -	722 (72)	- -
Vomiting*	390 (40)	59 (6)	221 (22)	7 (1)
Nausea*	883 (90)	78 (8)	749 (75)	15 (1)
Fatigue*	975 (99)	297 (30)	971 (97)	245 (24)
Peripheral edema*	599 (61)	25 (3)	670 (67)	26 (3)

Mean relative dose per cycle



- Calculated as actual/planned mg/m^2
- Similar relative dose of EC and DC in cycle 1 to 3
- The relative dose of docetaxel was 0.84 in cycle 6 compared to 0.88 of DC.

Conclusion 1

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- EC followed by docetaxel did not demonstrate any overall significantly superior efficacy compared to DC in patients with early and TOP2A normal breast cancer.
- A possible greater benefit from EC-D was demonstrated in patients with Grade 1-2 tumors and from DC in patients with Grade 3 tumors.
- A possible greater benefit from EC-D was demonstrated in postmenopausal patients and from DC in premenopausal patients.
- Patients more often reported adverse events following EC-D as compared to DC.

Acknowledgements

- The 2012 Danish women who participated
- The study nurses and investigators
- The Danish Breast Cancer Cooperative Group
- Danish Foundation for Clinical and Experimental Cancer Research
- Sanofi

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