Final Analysis of the Randomized DBCG 07-READ Trial

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Adjuvant Docetaxel and Cyclophosphamide With or Without Epirubicin for Early Breast Cancer: Final Analysis of the Randomized DBCG 07-READ Trial

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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

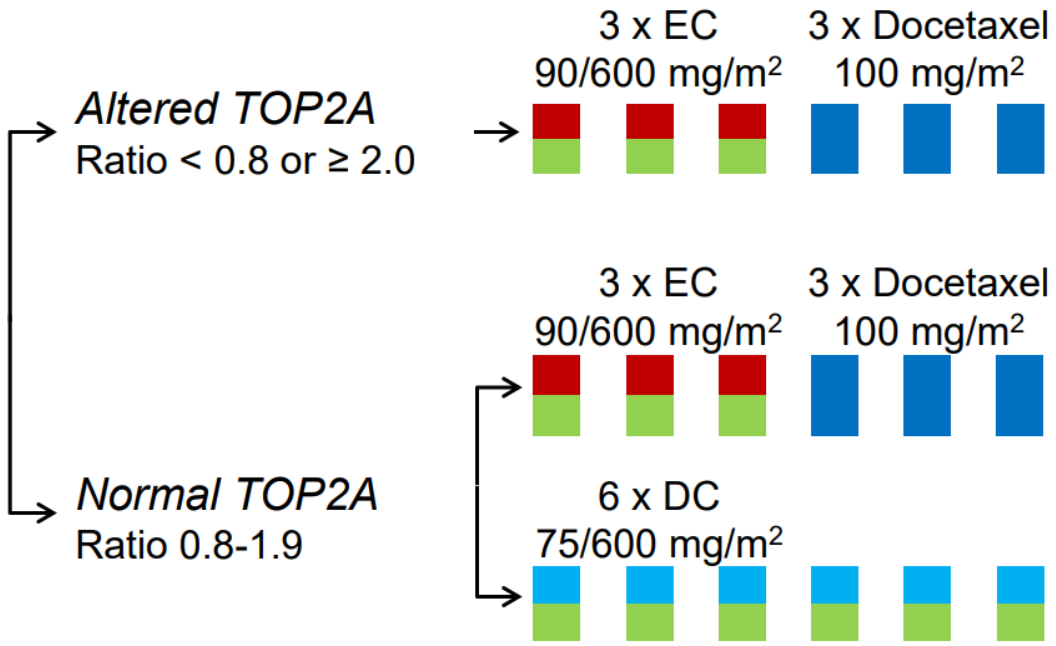
The aim of the trial is to test the hypothesis from the previous DBCG 89D trial of CMF versus CEF that patients with TOP2A normal tumors will derive no benefit from anthracycline

Eligible N=7687

TOP2A tested N=5160

TOP2A altered N=867
TOP2A normal N=4325

Randomized N=2012



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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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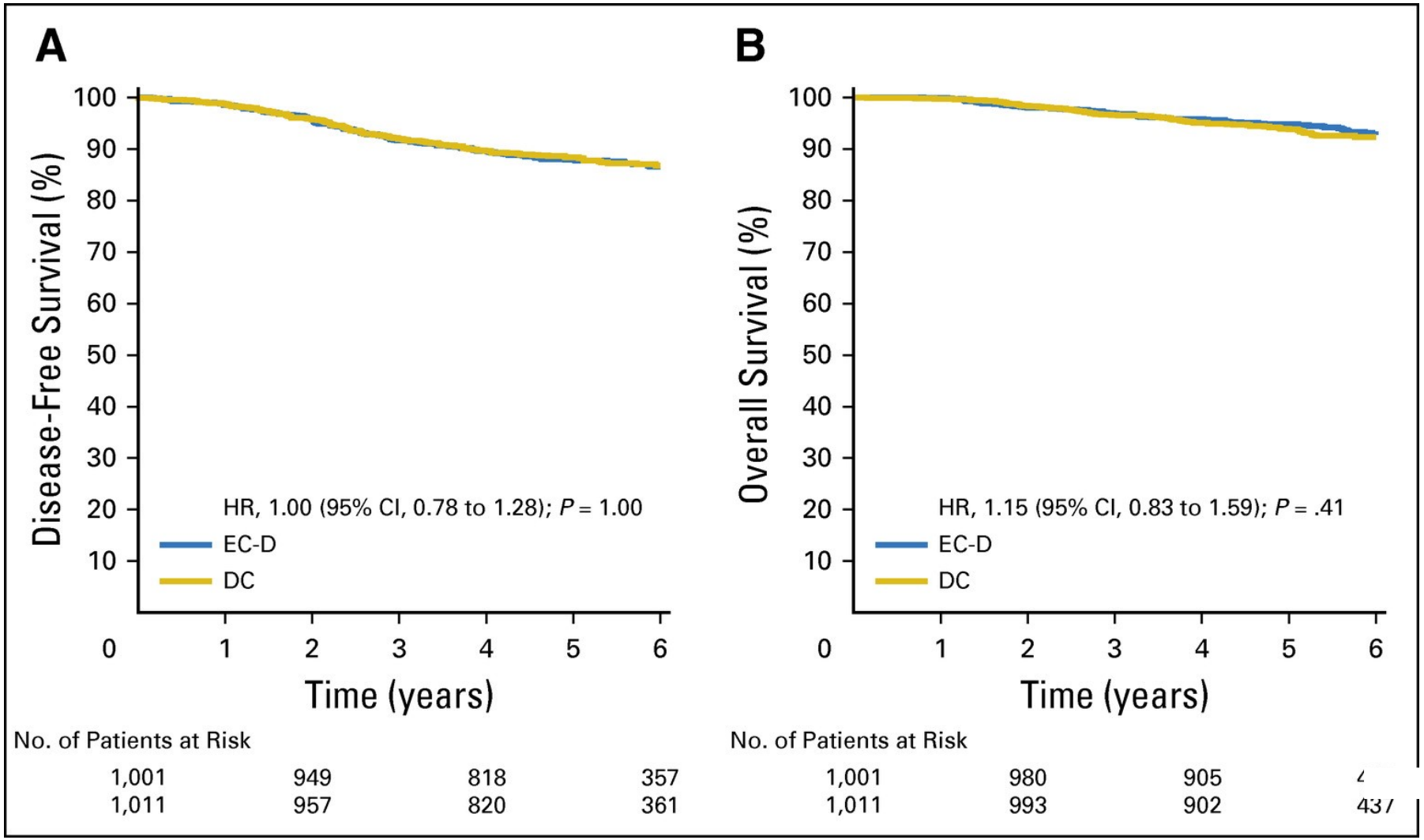
Median follow-up 69 mo's



Conclusion

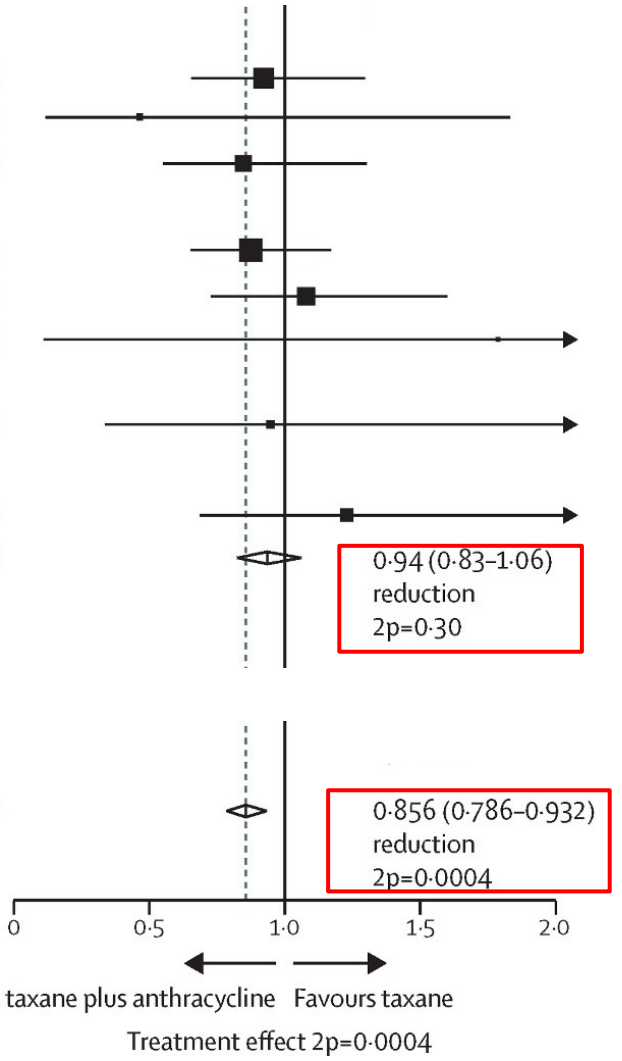
- No overall outcome benefit from adjuvant anthracyclines in patients with early *TOP2A*-normal breast cancer
- EC-D had a less favorable toxicity profile
- Two patients in the EC-D group developed acute myeloid leukemia

EBCTCG meta-analysis

Lancet 2023 (2019)

Recurrence of breast cancer (LR/DM/CBC)

	Cumulative doses		Events per participants (%)		Taxane plus anthracycline events†		Ratio of annual event rates (99% CI or 95% CI)
	Taxane	Anthracycline	Allocated taxane plus anthracycline	Allocated taxane	Log-rank O–E	Variance of O–E	Taxane plus anthracycline:taxane
(b) Sequential taxane plus anthracycline versus higher cumulative dose docetaxel plus cyclophosphamide							
2008 DBCG 07 READ	(3**E**90**C**600;3**D**100 *vs* 6**D**75**C**600)**q3**	D300 *vs* D450	E270	120/1001	123/1011	-4·7	57·4
2009 Kanagawa Japan	(3**FE**100**C**500;3**D**100 *vs* 6**D**75**C**600)**q3**‡	D300 *vs* D450	E300	5/53	10/50	-2·7	3·5
2009 NSABP B-49	(4**A**60**Cq2/q3**;12**P**80**q1**/4**P**175**q2**)/ (6**A**50**D**75**C**500**q3**) *vs* 6**D**75**C**600**q3**	D450/**P**700–960 *vs* D450	A240–300	69/932	80/938	-6·0	35·9
2009 LMU SUCCESS C	(3**FE**100**C**500;3**D**100 *vs* 6**D**75**C**600)**q3**	D300 *vs* D450	E300	155/1816	174/1827	-10·5	78·0
2009 WSG PlanB	(4**E**90**C**600;4**D**100 *vs* 6**D**75**C**600)**q3**	D400 *vs* D450	E360	94/1227	89/1222	3·2	42·9
2009 JBCRG-10†	(4**D**75**C**600**Trz**;4**FE**100**C**500 or v.v *vs* 6**D**75**C**600**Trz**)**q3**‡	D300 *vs* D450	E300	4/42	2 (1/25)	0·5	0·9
2009 JBCRG-09†	(3**D**75**C**600;3**FE**100**C**500 or v.v *vs* 6**D**75**C**600)**q3**‡	D225 *vs* D450	E300	18/128	2 (10/67)	-0·3	6·2
2010 MASTER,Fudan	(3**FE**100**C**500;3**D**100 *vs* 6**D**75**C**600)**q3**	D300 *vs* D450	E300	45/523	37/524	4·0	19·6
Subtotal				**510/5722 (8·9%)**	**535/5756 (9·3%)**	**-16·3**	**244·3**
Total (a+b+c+d)				**1062/9076 (11·7%)**	**1210/9119 (13·3%)**	**-82·0**	**528·7**



Heterogeneity between 4 subtotals: χ^2=16·5; p=0·0009

Heterogeneity within subtotals: χ^2=15·4; p=0·22

Heterogeneity between 16 trials: χ^2=31·9; p=0·0066

99% CI

95% CI

- Recurrence rates were 14% lower on average

  (RR 0·86, 95% CI 0·79– 0·93; p=0·0004)

  with taxane regimens including anthracycline than those without

- No significant reduction in recurrence risk for sequential schedules of taxane plus anthracycline when compared with DC

  (RR 0·94, 0·83–1·06; p=0·30)

  benefit primarily in patients with concurrent taxane and anthracycline

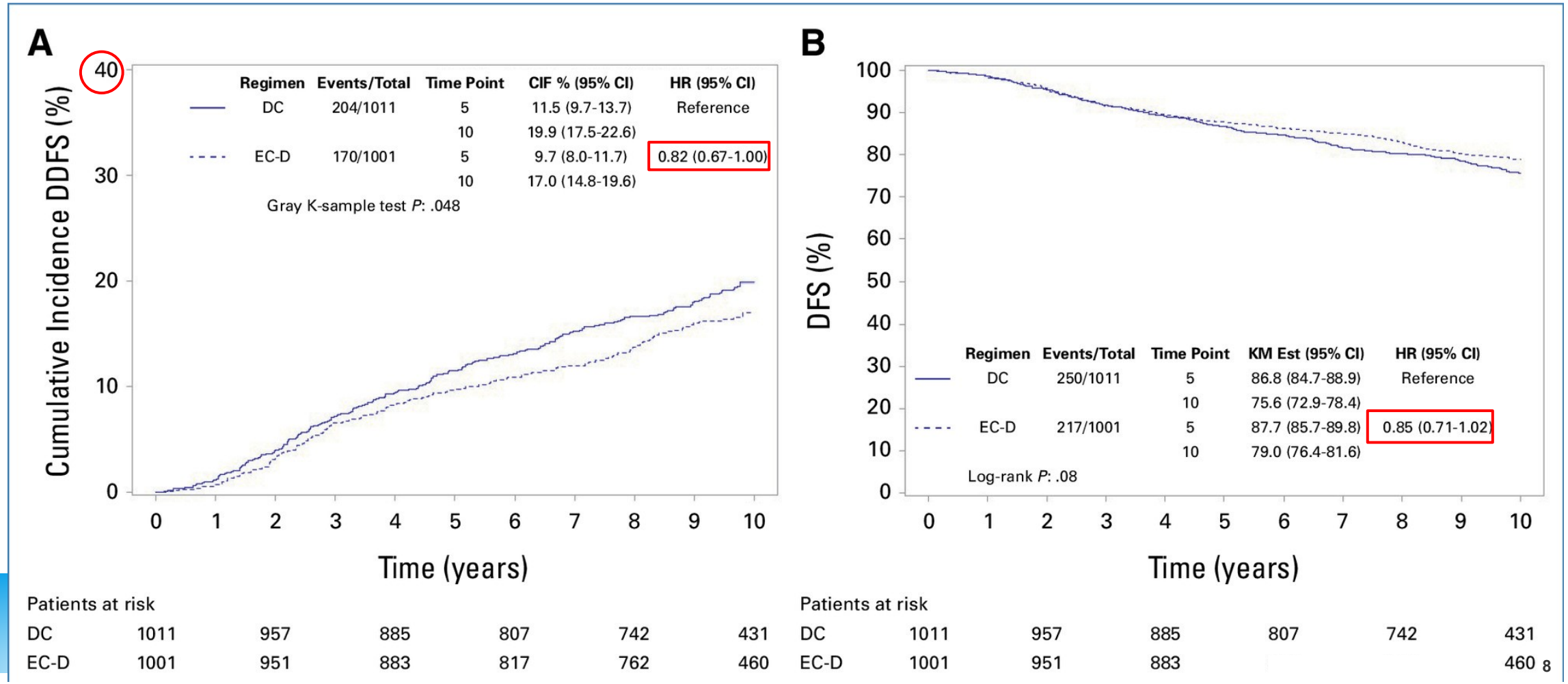
- There was one additional acute myeloid leukaemia case per 700 women treated

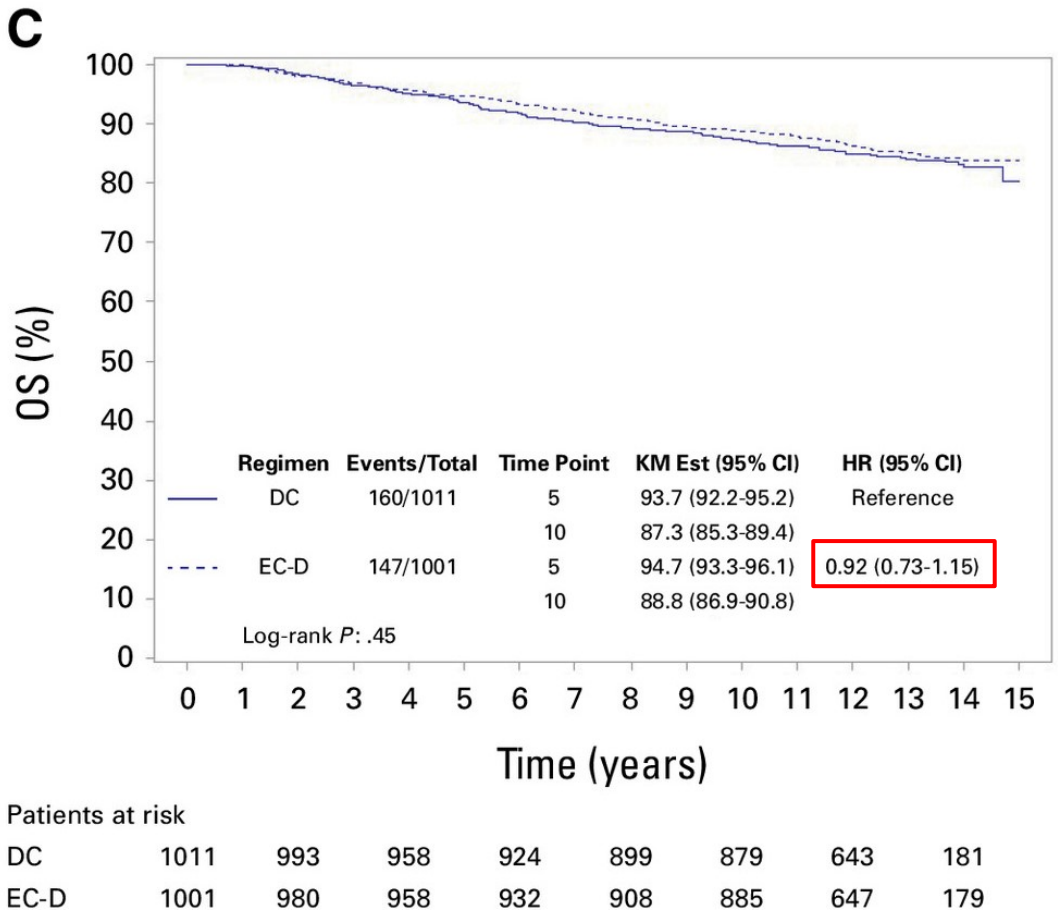
Final Analysis of the Randomized DBCG 07-READ Trial

- An update on the READ trial with 10 years of follow-up

DDFS; distant recurrence, death from any cause, or second (nonbreast) invasive cancer

DFS; any first event of invasive ipsilateral or contralateral breast recurrence, local or regional invasive recurrence, distant recurrence, second (nonbreast) invasive cancer, or death from any cause

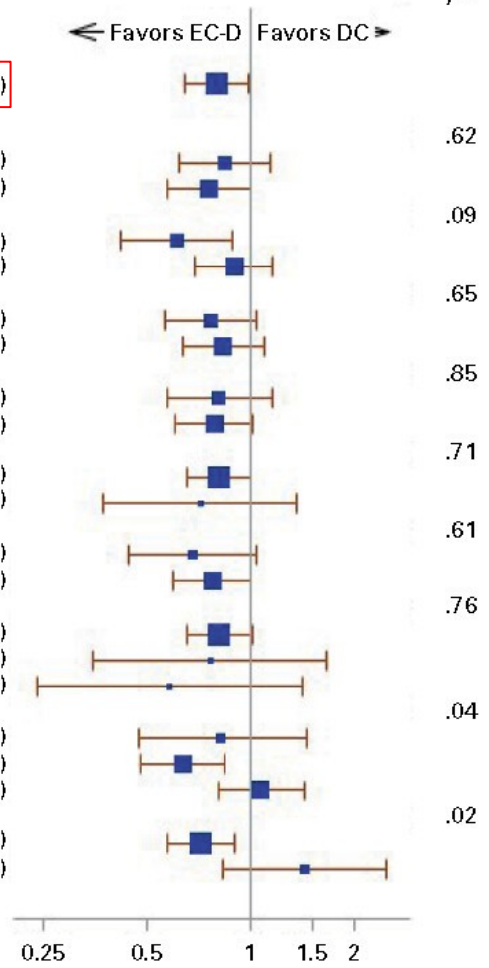




Anthracycline-based adjuvant chemotherapy was found to significantly reduce the risk of breast cancer recurrence without significantly affecting all-cause mortality

A

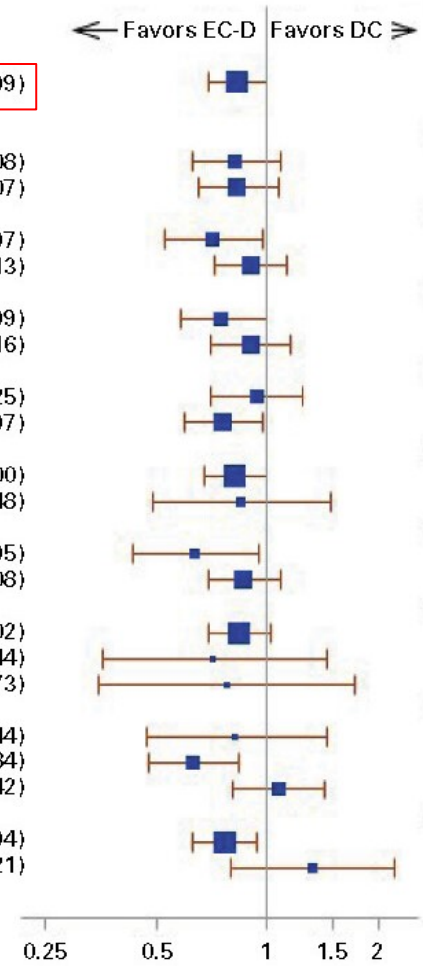
DDFS	EC-D Events/N	DC Events/n	HR (95% CI)	P*
All	170/1001	204/1011	0.79 (0.64, 0.98)	
Menopausal status				.62
Pre	77/508	100/544	0.84 (0.62, 1.14)	
Post	93/493	104/467	0.75 (0.57, 1.00)	
Nodal status				.09
Negative	45/448	74/467	0.61 (0.42, 0.88)	
Positive	125/553	130/544	0.90 (0.69, 1.15)	
Tumor size				.65
0-20 mm	76/618	84/579	0.76 (0.56, 1.03)	
>20 mm	94/383	120/432	0.83 (0.63, 1.10)	
ER				.85
0-9 %	68/299	67/273	0.81 (0.57, 1.16)	
10-100 %	102/702	137/738	0.78 (0.60, 1.01)	
HER2				.71
Normal	152/888	180/902	0.80 (0.65, 1.00)	
Amplified	18/113	24/109	0.71 (0.37, 1.35)	
Ki-67				.61
0-14 %	34/307	51/325	0.68 (0.44, 1.04)	
>14 %	114/588	133/568	0.77 (0.59, 1.00)	
Histologic type				.76
Ductal	151/873	176/871	0.81 (0.65, 1.01)	
Lobular	11/72	16/87	0.76 (0.35, 1.64)	
Other	8/56	12/53	0.58 (0.24, 1.40)	
Malignancy grade				.04
I	19/159	23/176	0.82 (0.47, 1.44)	
II	62/453	93/459	0.63 (0.48, 0.84)	
III	80/328	75/311	1.07 (0.81, 1.42)	
TOP2A/CEN17 ratio				.02
<1.5	135/842	182/871	0.71 (0.57, 0.89)	
≥1.5	35/159	22/140	1.43 (0.83, 2.46)	



*Test of interaction between treatment and subgroup, unadjusted for multiplicity.

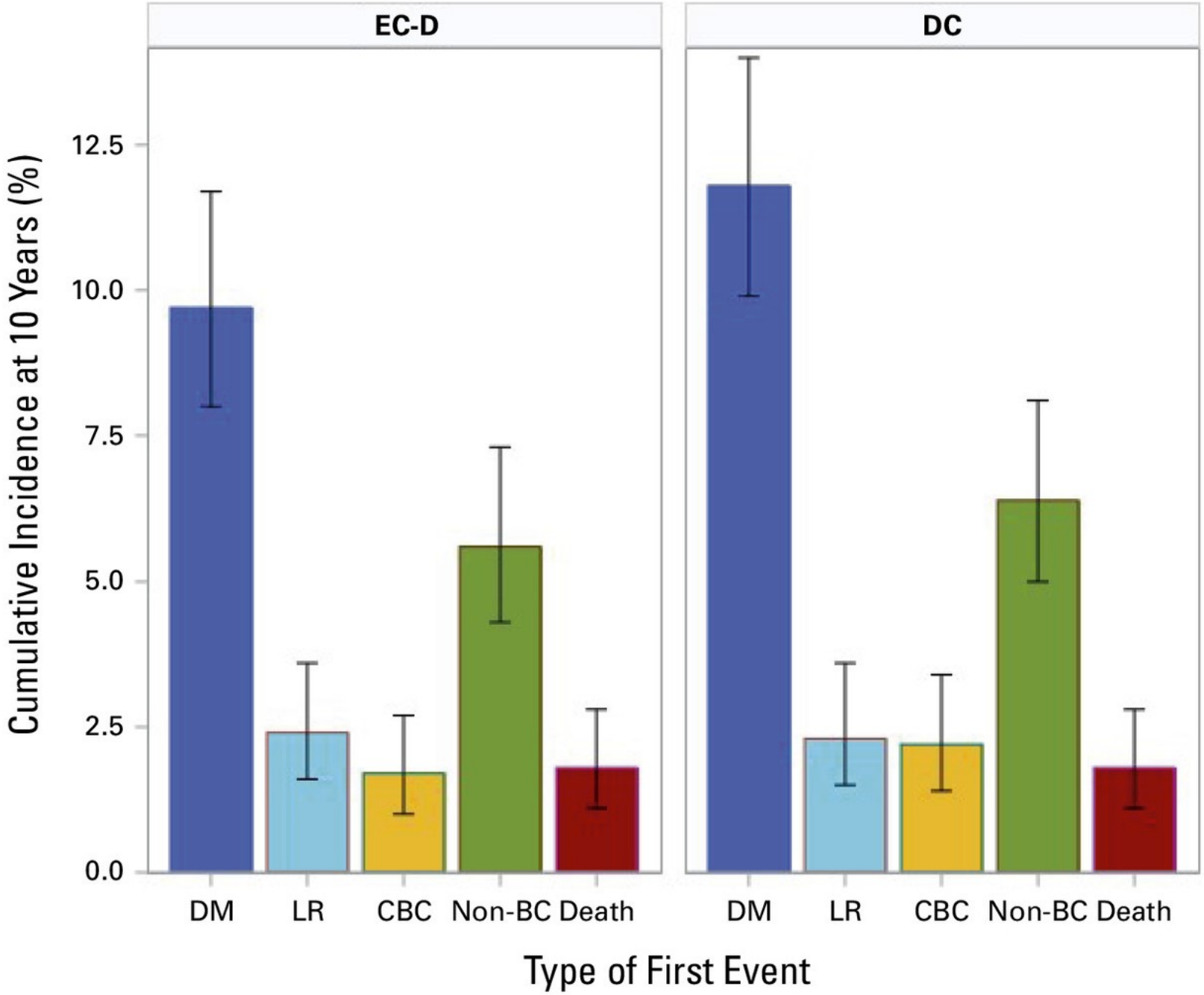
B

DFS	EC-D Events/N	DC Events/n	HR (95% CI)	P*
All	217/1001	250/1011	0.83 (0.69, 0.99)	
Menopausal status				.93
Pre	93/508	123/544	0.82 (0.63, 1.08)	
Post	124/493	127/467	0.83 (0.65, 1.07)	
Nodal status				.23
Negative	71/448	100/467	0.71 (0.53, 0.97)	
Positive	146/553	150/544	0.90 (0.72, 1.13)	
Tumor size				.34
0-20 mm	102/618	113/579	0.75 (0.58, 0.99)	
>20 mm	115/383	137/432	0.90 (0.70, 1.16)	
ER				.29
0-9 %	96/299	87/273	0.93 (0.70, 1.25)	
10-100 %	121/702	163/738	0.76 (0.60, 0.97)	
HER2				.91
Normal	193/888	223/902	0.82 (0.68, 1.00)	
Amplified	24/113	27/109	0.85 (0.49, 1.48)	
Ki-67				.19
0-14 %	42/307	65/325	0.64 (0.43, 0.95)	
>14 %	152/588	161/568	0.86 (0.59, 1.08)	
Histologic type				.90
Ductal	193/873	216/871	0.84 (0.69, 1.02)	
Lobular	13/72	20/87	0.71 (0.36, 1.44)	
Other	11/56	14/53	0.78 (0.35, 1.73)	
Malignancy grade				.04
I	22/159	27/176	0.82 (0.47, 1.44)	
II	77/453	119/459	0.63 (0.48, 0.84)	
III	105/328	88/311	1.07 (0.81, 1.42)	
TOP2A/CEN17 ratio				.05
<1.5	179/842	225/871	0.77 (0.63, 0.94)	
≥1.5	38/159	25/140	1.33 (0.80, 2.21)	



*Test of interaction between treatment and subgroup, unadjusted for multiplicity.

REGION

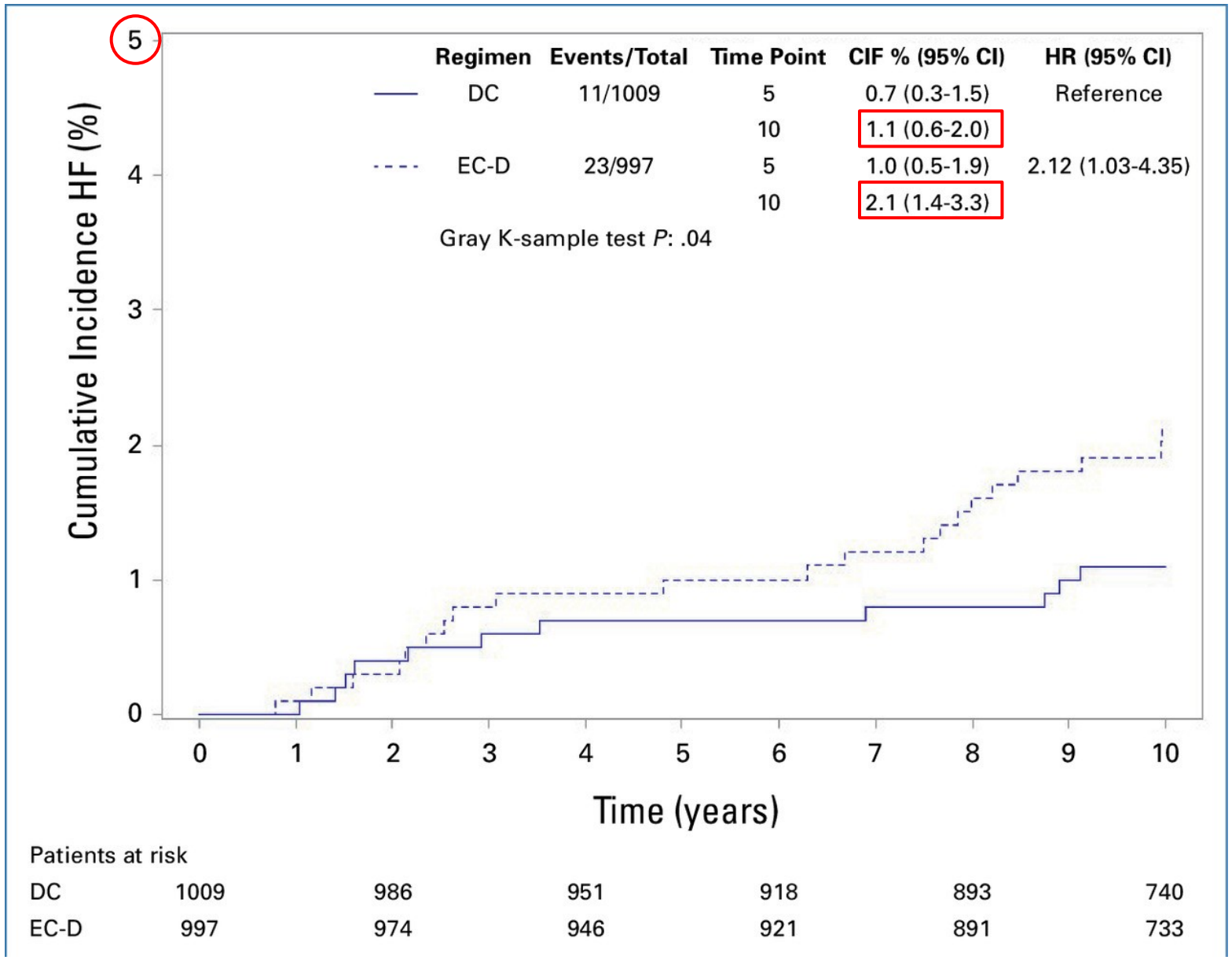

EC-D
DC
Cumulative Incidence at 10 Years (%)
12.5
10.0
7.5
5.0
2.5
0.0
DM
LR
CBC
Non-BC Death
DM
LR
CBC
Non-BC Death
Type of First Event

Second non–breast invasive cancer

	Treatment Arm: No of Patients (%)	
	EC-D (n = 1,001)	**DC (n = 1,011)**
	61 pt.s (6%)	76 pt.s (8%)
GI	15	16
Pancreas	2	4
Lung	18	13
Kidney	1	2
Gynecological	8	20
Malignant melanoma	6	10
Sarcoma	6	2
Head and neck	6	4
Leukemia	**2**	**3**
Lymphoma	2	5
Bone	1	0

2 acute myeloid leukemia vs 1 AML, 2 cronic leukemia

Incident **Heart Failure** developed in 34 patients:
23 patients in the EC-D group and 11 patients in the DC group.



Cardiac Risk Factors

	Treatment Arm; No (%)				Subdistributional Hazards Estimates		
	EC-D (N=997)		DC (N=1009)				
	Events	(%)	Events	(%)	HR	(95% CI)	P
Epirubicin							
Yes	23	(2.3)			2.12	(1.03-4.35)	0.04
No			11	(1.1)			
Trastuzumab							
Yes (110/108)	2	(1.8)	2	(1.9)	1.08	(0.38-3.08)	0.88
No (887/901)	21	(2.4)	9	(1.0)	Ref.		
Left sided RT							
Yes (457/429)	10	(2.2)	5	(1.2)	1.00	(0.51-1.96)	0.99
No (540/580)	13	(2.4)	6	(1.0)	Ref.		
BMI (kg/m²)							
<25 (549/544)	10	(1.8)	5	(0.9)	Ref.		
25-30 (272/305)	5	(1.8)	2	(0.7)			
>30 (176/160)	8	(4.6)	4	(2.5)	2.73	(1.35-5.51)	<0.01
Diabetes							
Yes (21/21)	2	(9.5)	0	(0.0)	2.89	(0.71-11.8)	0.14
No (976/988)	21	(2.2)	11	(1.1)	Ref.		
Hypertension							
Yes (84/85)	3	(3.6)	0	(0.0)	1.05	(0.32-3.42)	0.94
No (913/924)	20	(2.2)	11	(1.2)	Ref.		
High cholesterol							
Yes (23/20)	**3**	**(13.0)**	0	(0.0)	4.53	(1.40-14.7)	0.01
No (974/989)	**20**	**(2.1)**	11	(1.1)	Ref.		

Conclusion

- In contrast to the first analysis, anthracycline-based chemotherapy was seen to reduce the risk of recurrence, but not significantly affecting all-cause mortality

- The risk of HF was doubled in patients receiving anthracycline; the overall risk of HF was low and the absolute risk of HF was increased by 1 percentage point following EC-D without increasing mortality from HF; Six of the 11 patients who developed HF after DC died during follow-up compared with 5 of 23 patients with HF after EC-D