DBCG

Adjuverende endokrin terapi

Ann Knoop

1977
40
2017
DBCG

16th ACTA ONCOLOGICA SYMPOSIUM

Endokrin behandling i DBCG

Program	Menopause status	
	Præ	**Post**
77	0	0
82	0	TAM 1 år
89	0	TAM 1-5 år
99 og 01	TAM 5 år	TAM 5 år
07	TAM 5 år	AI 5 år (jan 09)
10	Endokrin behandling, hvis ER > 1%	
13	TAM i 10 år	AI 5 år og yderligere AI til N+, hvis TAM i 5 år
15	OvS + TAM/AI hvis < 35 år og "høj-risiko"	AI 5 år

Jensen MB, Acta Oncol. 2018 Jan;57(1):13-18

at også bare lidt behandling gavner…….

LÆNGERE OG LÆNGERE BEHANDLINGER…

ORIGINAL ARTICLE

Two years of tamoxifen or no adjuvant systemic therapy for patients wit high-risk breast cancer: long-term follow-up of the Copenhagen breast cancer trial

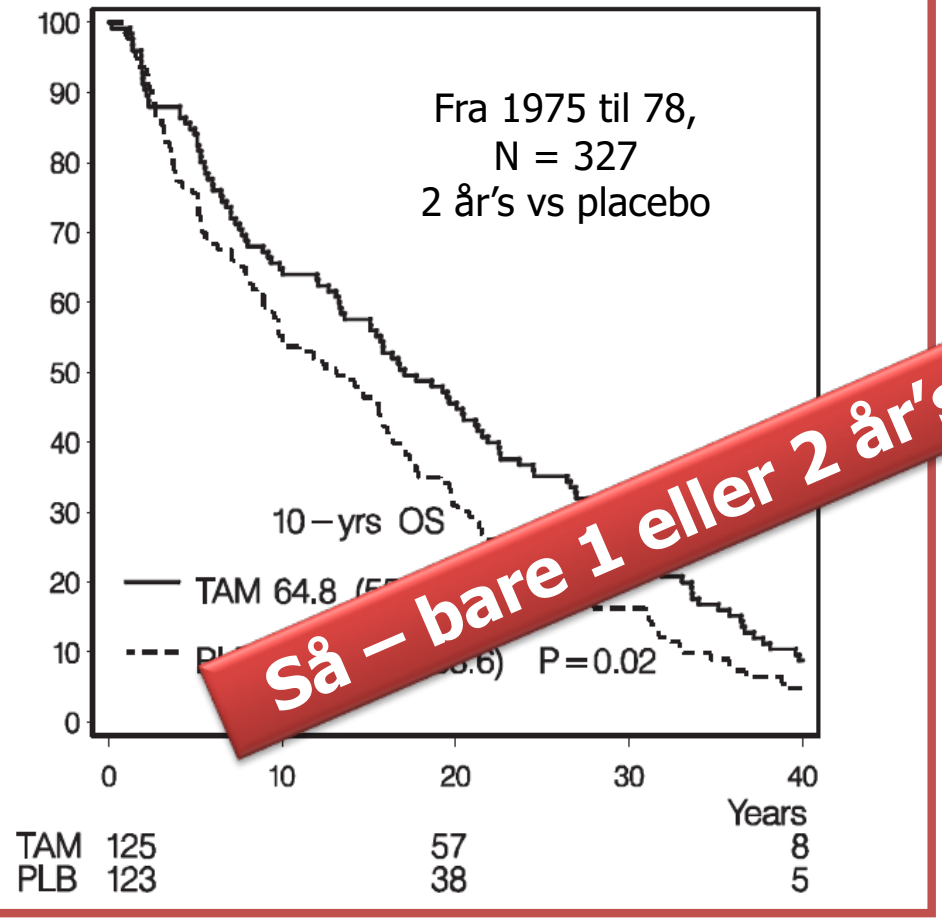
Acta Oncol 2018 Jan;57(1):26-30

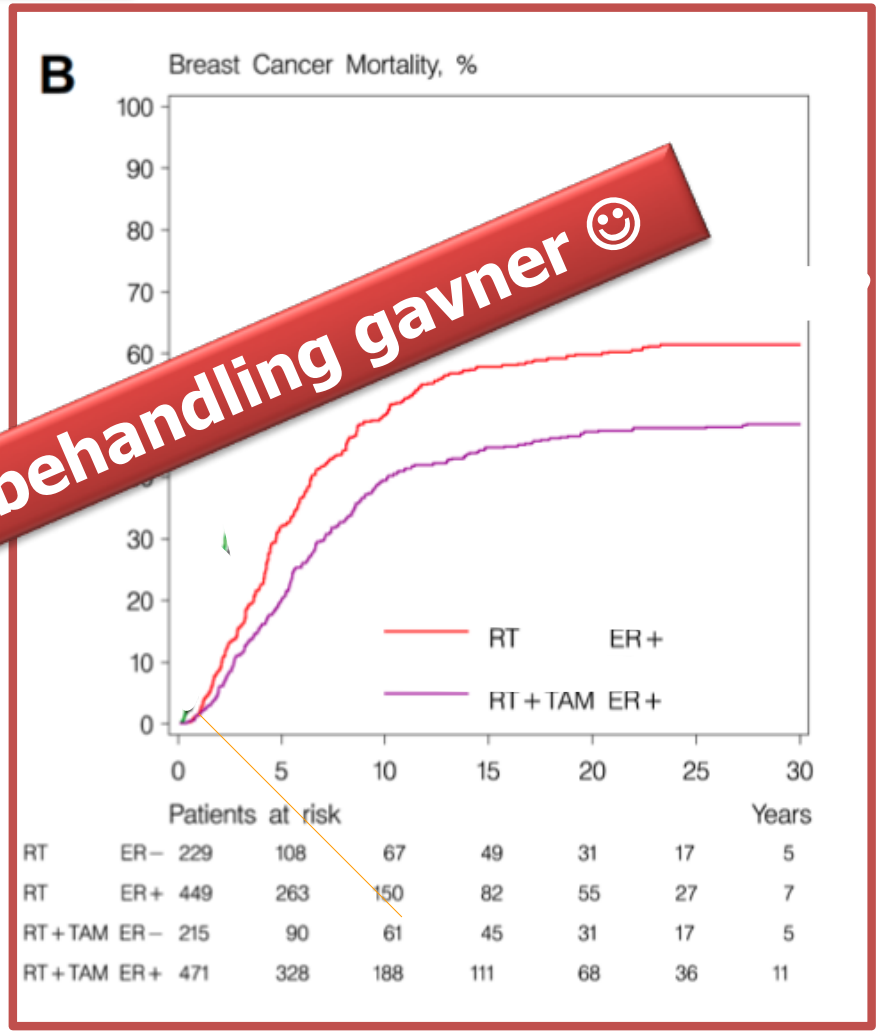
Maj-Britt Jensen[a], Jens Fabricius Krarup[a], Torben Palshof†, Henning T. Mouridsen[a] and Bent Ejlertsen

Estrogen receptor, Progesterone receptor, HER2 status and Ki67 index and responsiveness to adjuvant tamoxifen in postmenopausal high-risk breast cancer patients enrolled in the DBCG 77C trial

Eur J of Cancer 2014,

Ann S. Knoop[a,b,e], Anne-Vibeke Lænkholm[g], Maj-Britt Jensen[c], Kirsten V. Nielsen[d], Jørn Andersen[e], Dorte Nielsen[f], Bent Ejlertsen[b,c], for the Danish Breast Cancer Cooperative Group



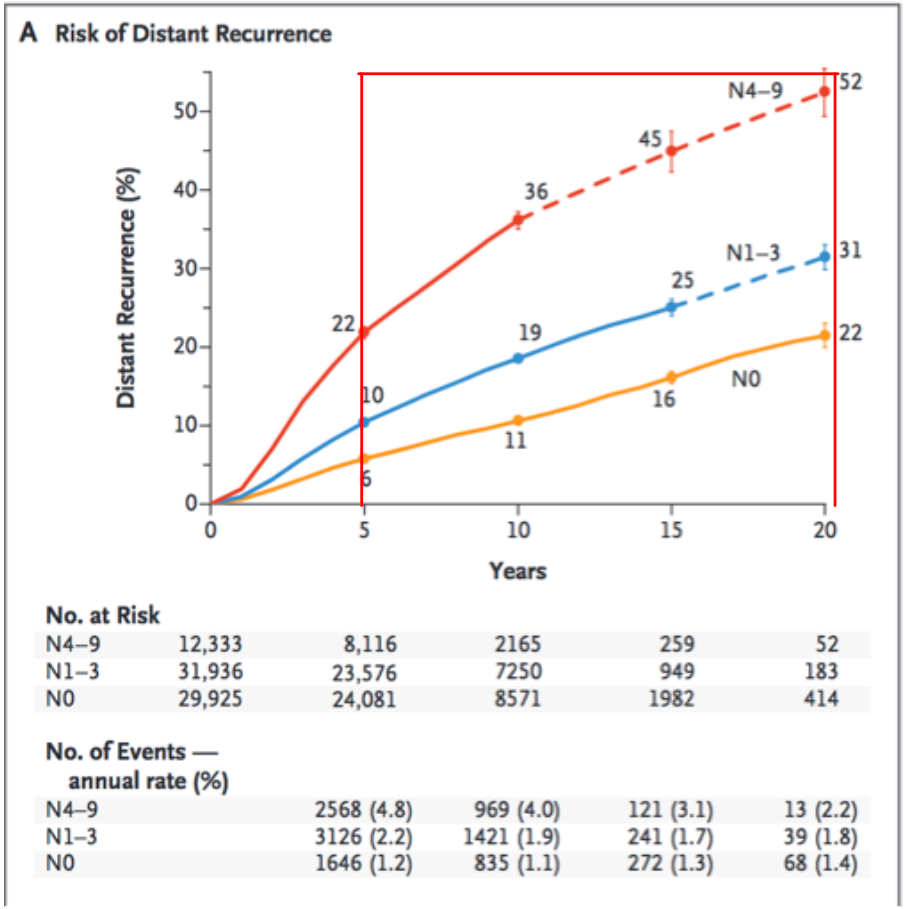


Så – bare 1 eller 2 år's behandling gavner ☺

Rose C, et, al. Breast Cancer Res Treat 1983.
Rose C, et al. Lancet 1985

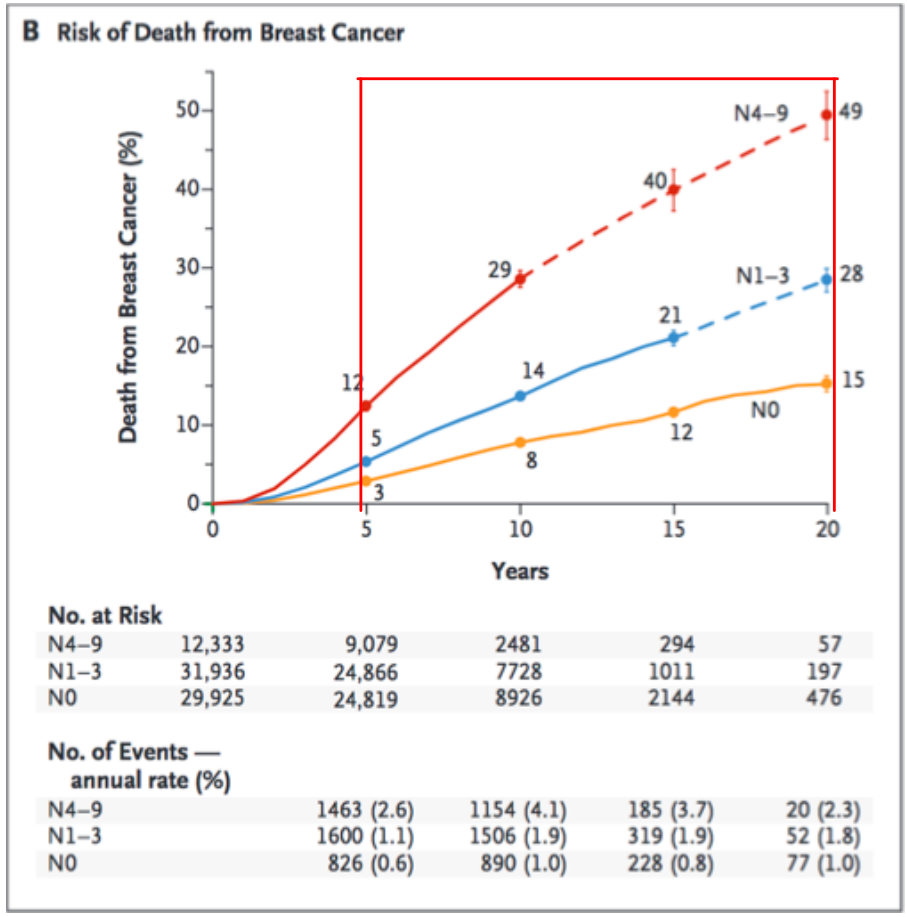

FYS
CONCENTRATE
Global
HD

Risiko for fjern recidiv eller død af brystkræft gennem en 20 års periode



No. at Risk					
N4–9	12,333	8,116	2165	259	52
N1–3	31,936	23,576	7250	949	183
N0	29,925	24,081	8571	1982	414

No. of Events — annual rate (%)				
N4–9	2568 (4.8)	969 (4.0)	121 (3.1)	13 (2.2)
N1–3	3126 (2.2)	1421 (1.9)	241 (1.7)	39 (1.8)
N0	1646 (1.2)	835 (1.1)	272 (1.3)	68 (1.4)



No. at Risk					
N4–9	12,333	9,079	2481	294	57
N1–3	31,936	24,866	7728	1011	197
N0	29,925	24,819	8926	2144	476

No. of Events — annual rate (%)				
N4–9	1463 (2.6)	1154 (4.1)	185 (3.7)	20 (2.3)
N1–3	1600 (1.1)	1506 (1.9)	319 (1.9)	52 (1.8)
N0	826 (0.6)	890 (1.0)	228 (0.8)	77 (1.0)

Pan H et al: NEJM November 9, 2017

Siden 2008

Forlænget endokrin behandling og ovariel supression

ENDOKRIN BEHANDLING TIL PRÆ-MENOPAUSALE KVINDER MED BRYSTKRÆFT

TAMOXIFEN 10 VS. 5 ÅR

Tamoxifen længere end 5 år?

Studies of 5 vs. 10 years of Tamoxifen

Trial and Year	Number Randomized	Recruitment Period	Follow Up (years)
ECOG 1996	194	1982-1987	5.6
NSABP B-14 2001	1172	1987-1994	6.8
Scottish 2001	242	1985-1989	15
ATLAS 2012	6846	1996-2005	7.6
aTTOm 2013	6953	1991-2005	15

ATLAS (53%Erpos) & aTTom (40% Erpos)

Brystkræftpatienter, der efter 5 års behandling med tamoxifen – ikke havde tegn på recidiv

R

8% præ
90% post

Yderligere 5 år på TAM

	Tilbagefald efter 10 års behandling	Tilbagefald efter 15 år	Brystkræft dødelighed år 15
ATLAS	**1.4**	**2.7 (S)**	**3 (S)**
aTTom		**4 (S)**	**3 (NS)**
Tab #			**0.2%**

#;
endometrie cancer,
emboli

Estimeret absolut effekt på brystkræftdødelighed år 15 – 0 vs 10 år: 12%

Davies C et al. Lancet 2012
Gray et. al - ASCO 2013

Meta-analysis-1 (2013) - blandet tidligere endokrin behandling

N= 29.138			AI (7.584)	ABCSGa-6, MA17, B33
ER+:Hovedsalige Post menopausale pt.	5 års TAM 14.540			
			Tamoxifen (21.554)	ATLAS, Scottish, ECOG, B14

OS Odds Ratio 0.89

BCSS Odds Ratio 0.78

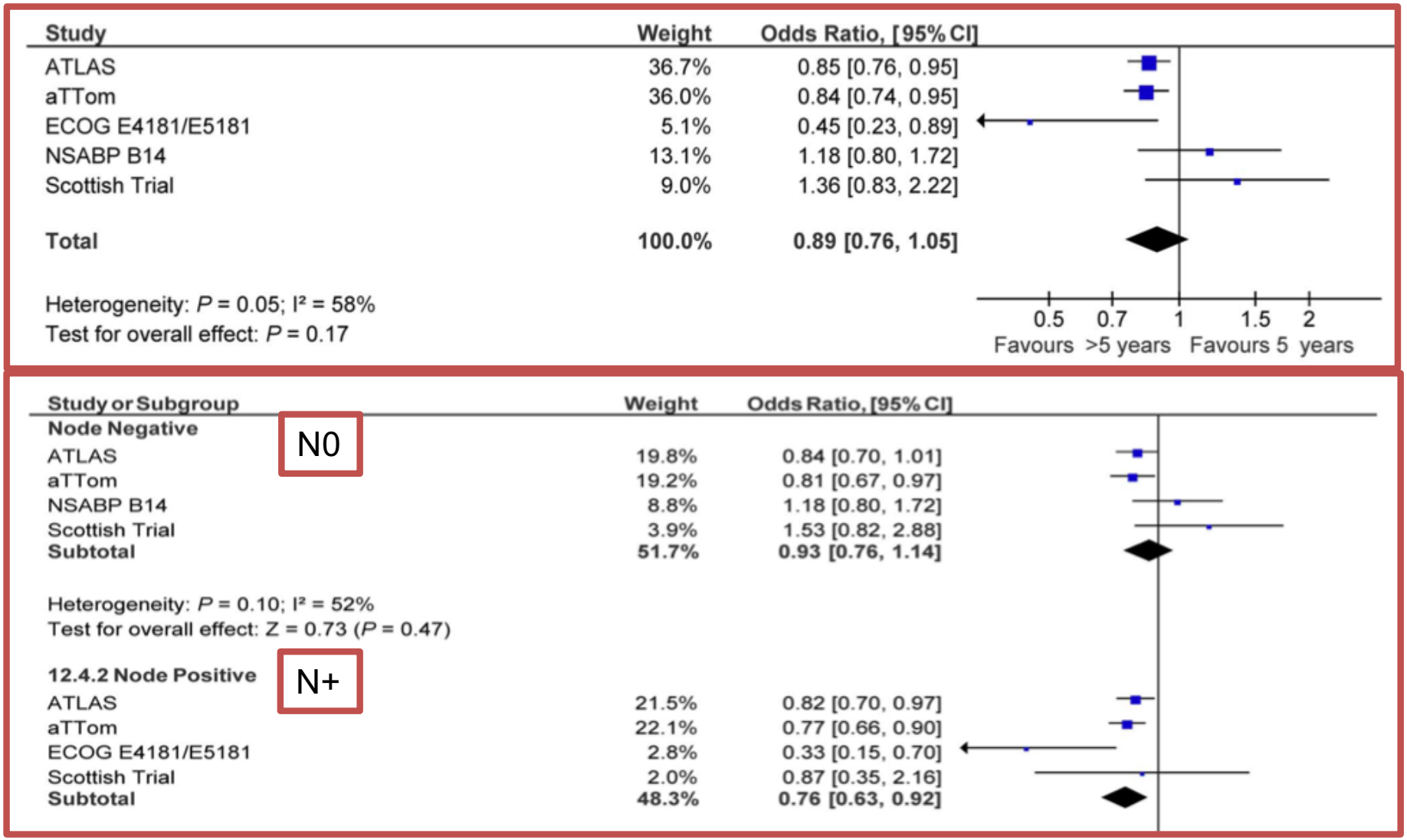
RFS Odds Ratio 0.72

Fjernrecidiver reduceret med 13%

Breast Cancer Res Treat 2013 Jul;140(2):233-40.

Meta-analysis-2 (2014) – kun tamoxifen

Breast Cancer Recurrence



Meta-analysis-2 (2014); absolut forskel 5 vs 10 år og NNT

Event	Ref	AR	NNT
Tilbagefald - alle	1-3	2	57
Tilbagefald (ER+)	1-3	3	38
Fjern metastaser	2	1	79

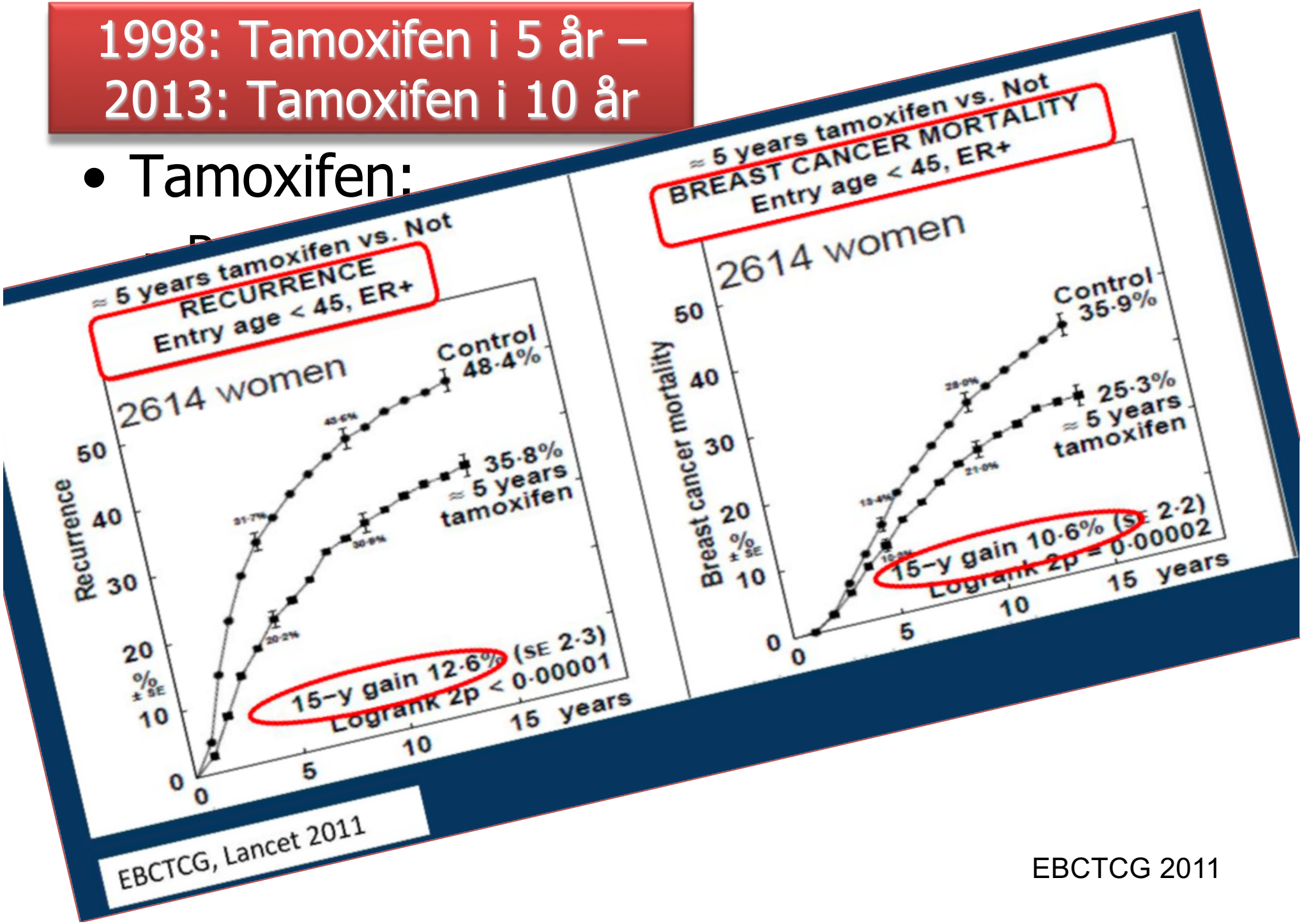
1: JNCI 93: 456-462: Scottish Trial
2: Lancet 12: ATLAS
3: EJC 13; abstract 1860: aTTom

PLOS ONE February 2014 | Volume 9 | Issue 2 | e88238

OVARIEL SUPRESSION OG ENDOKRIN BEHANDLING

1998: Tamoxifen i 5 år – 2013: Tamoxifen i 10 år

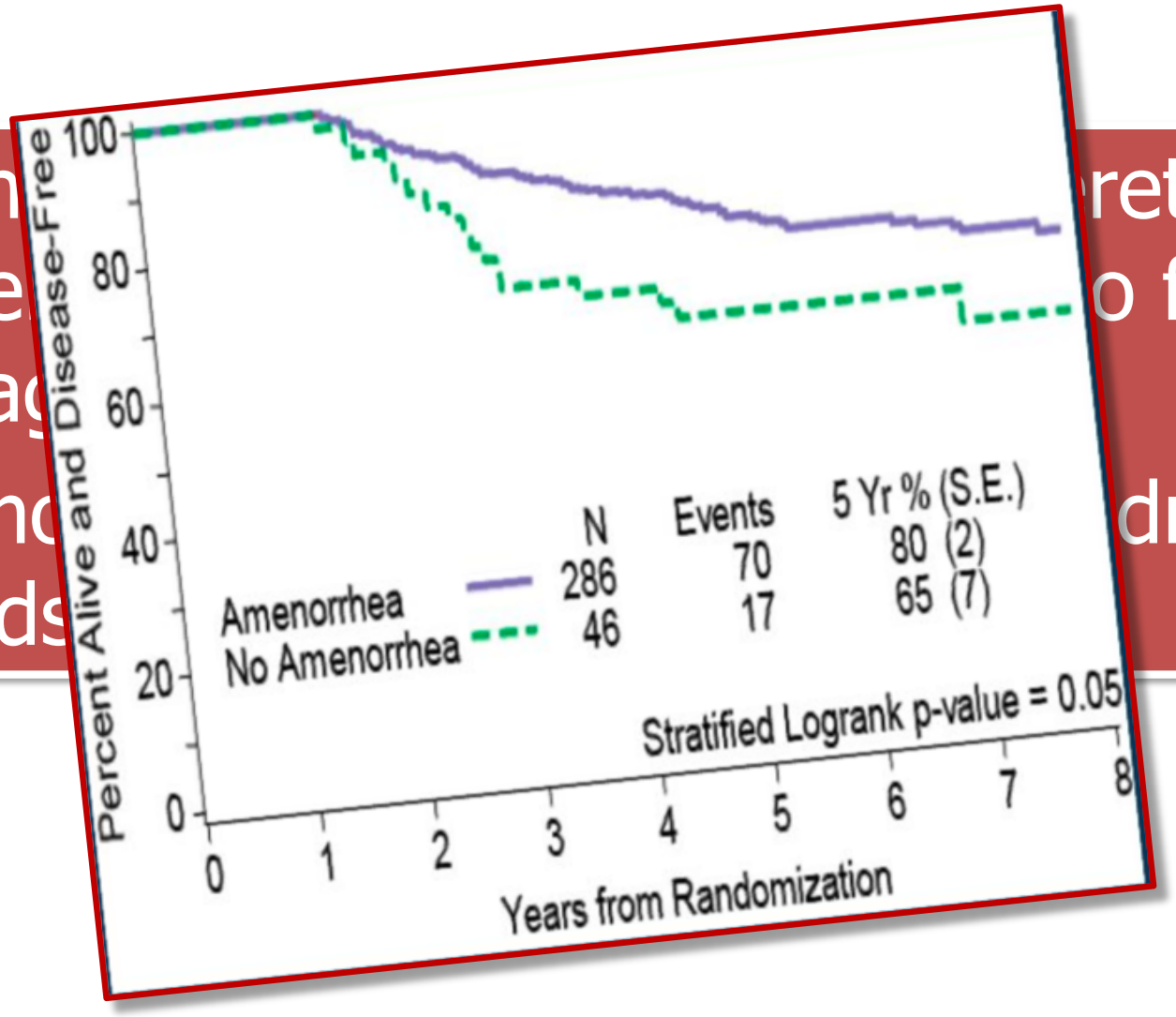
- Tamoxifen:



EBCTCG 2011

Baggrund for OvS (Ovariel Supression)

- Kvin… …ret
  ame… …o for
  tilba…
- Kemo… …dre
  sands…



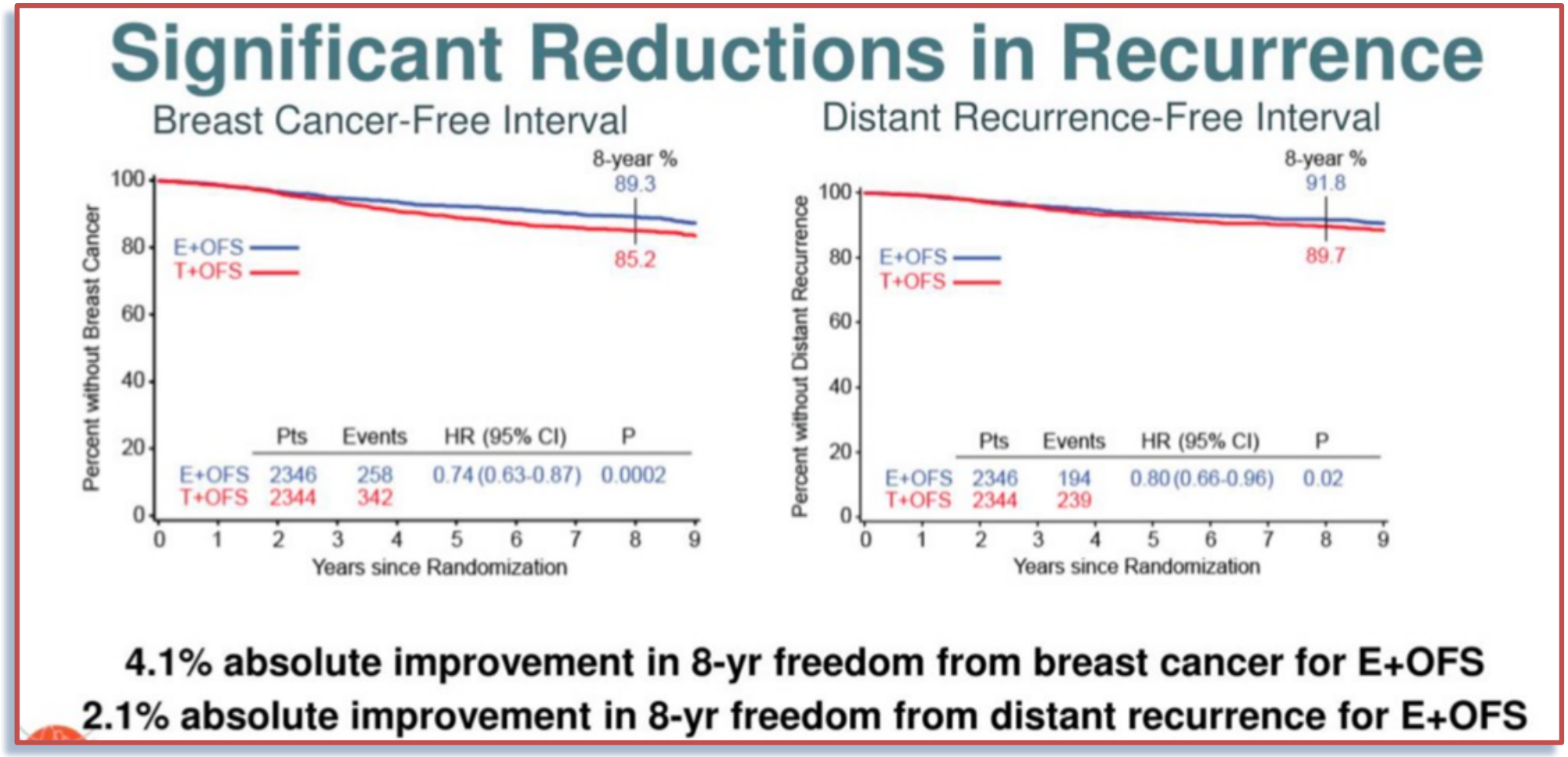
Pagani et al. Eur J Cancer 1998, IBCSG J Clin Oncol 2006, EBCTGS, Lancet 2007 Swain et al. NEJM 2010 89B, Ejlertsen et al. 2006 J Clin Oncol. Nov 1;24(31):4956-62.

TEXT & SOFT design N = 4690

PRÆ ERpos	**+/- kemo OVS start inden beh**	**TEXT: 2672**		**TAM + OFS 5 yr. ExE + OFS 5 yr.**
PRÆ ERpos	**1. Ingen kemo 2. Præ 8 mdr. efter op. og kemo**	**SOFT: 3063**	**R**	**1. TAM 2. TAM + OFS 5 yr. 3. ExE + OFS 5 yr.**

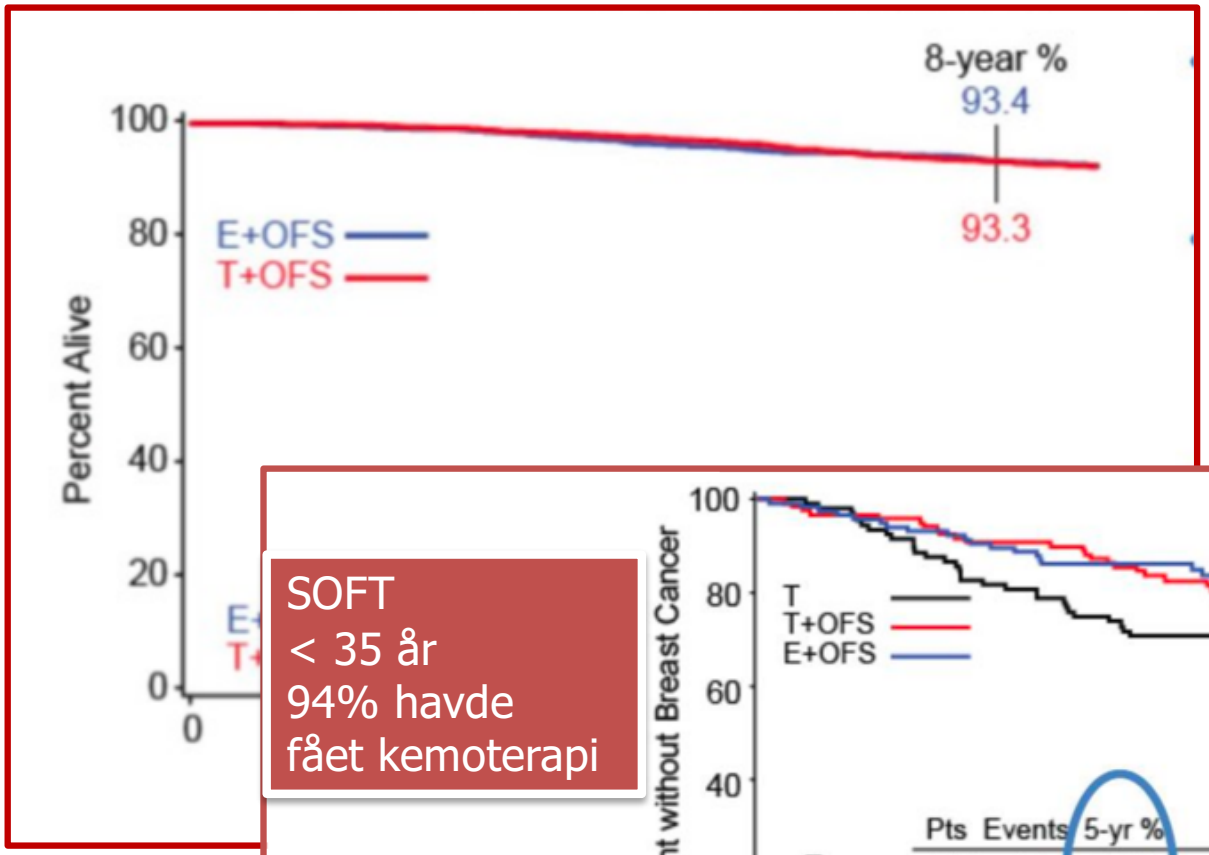
9 yrs follow-up – San Antonio dec. 2017

Joint analyses (TEXT & SOFT)



Flere endometrie cancer og trombose/embolier (grad 2-4) i TAM + OFS
Flere led/muskelsmerter, knogle-hændelser i AI + OFS

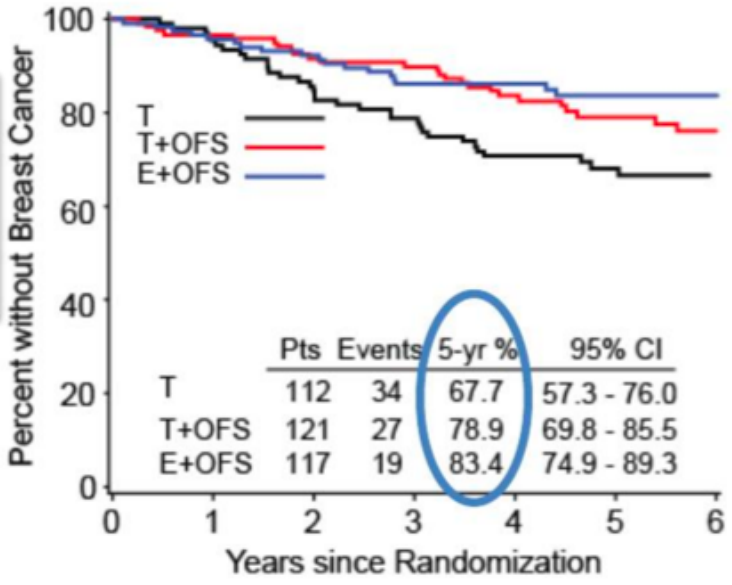
Joint analyses (TEXT & SOFT) OS



Ingen overlevelses gevinst

25% i AI
19% i TAM gruppen stoppede før tid

SOFT
< 35 år
94% havde fået kemoterapi



Siden 2008

AI (uanset hvilken) som primær behandling og evt. forlænget?

ENDOKRIN BEHANDLING TIL POST-MENOPAUSALE KVINDER MED BRYSTKRÆFT

VOLUME 35 · NUMBER 10 · APRIL 1, 2017

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

J Clin Oncol. 2017 Apr 1;35(10):1041-1048. doi: 10.1200/JCO.2016.69.2871. Epub 2017 Jan 23.

Comparative Efficacy and Safety of Adjuvant Letrozole Versus Anastrozole in Postmenopausal Patients With Hormone Receptor-Positive, Node-Positive Early Breast Cancer: Final Results of the Randomized Phase III Femara Versus Anastrozole Clinical Evaluation (FACE) Trial.

Smith I[1], Yardley D[1], Burris H[1], De Boer R[1], Amadori D[1], McIntyre K[1], Ejlertsen B[1], Gnant M[1], Jonat W[1], Pritchard KI[1], Dowsett M[1], Hart L[1], Poggio S[1], Comarella L[1], Salomon H[1], Wamil B[1], O'Shaughnessy J[1].

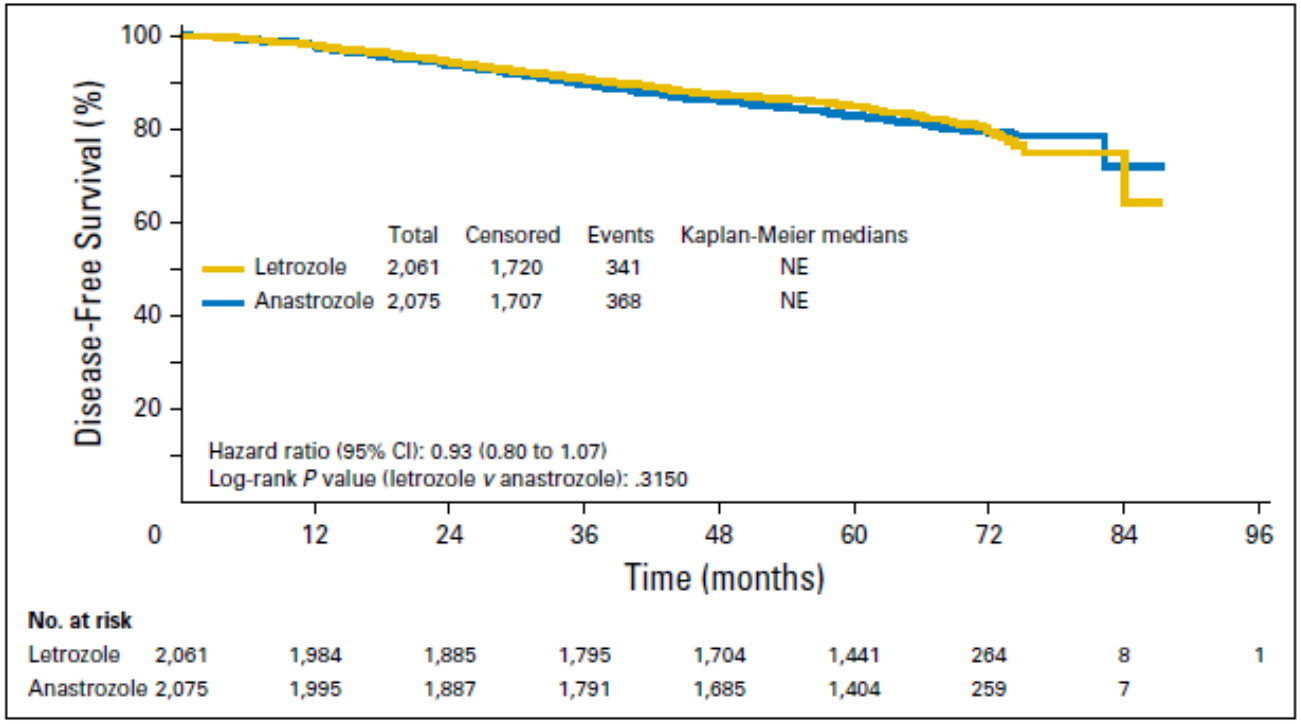
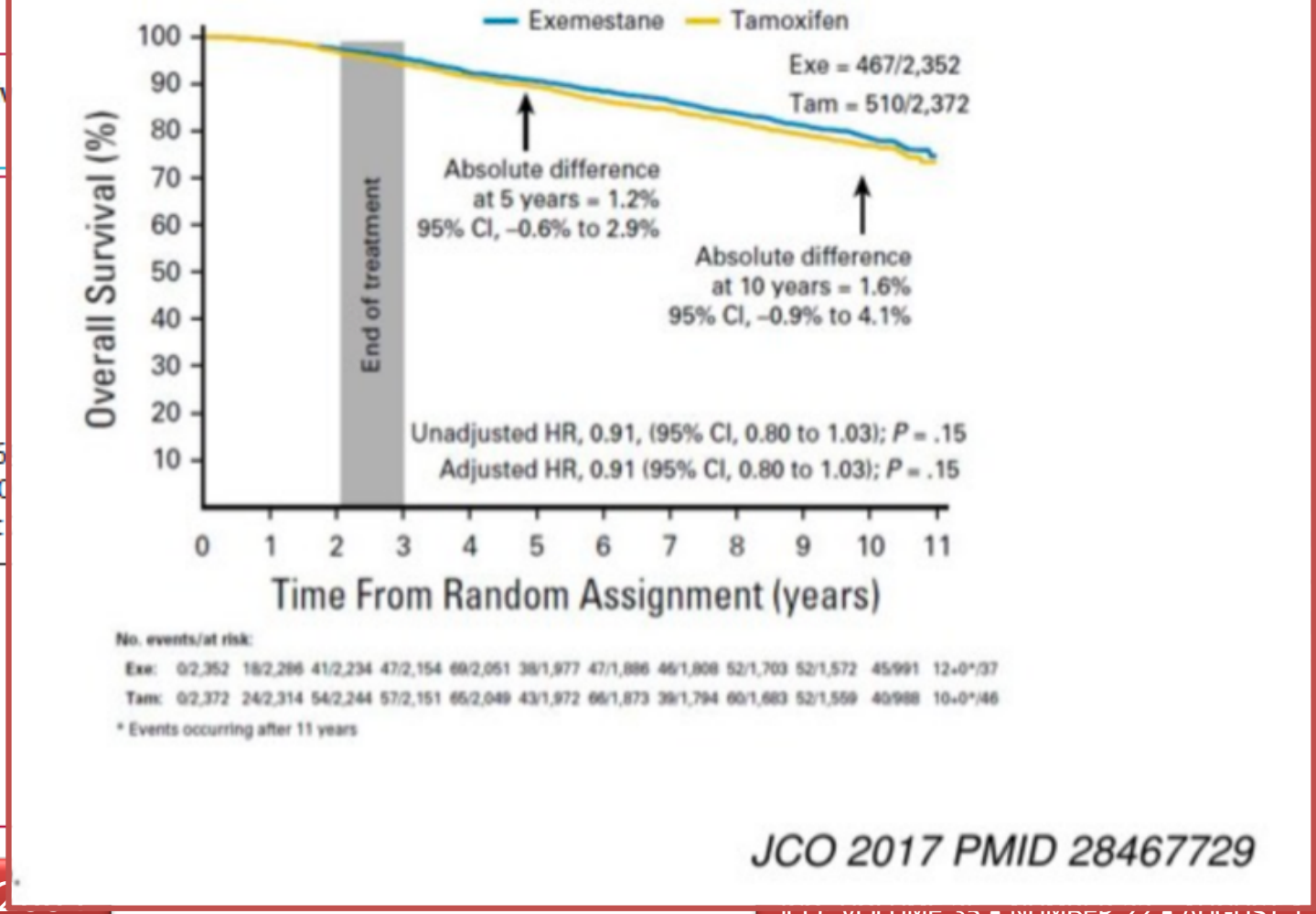


Fig 1. Disease-free survival. NE, non-evaluable.

Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a ra



JCO 2017 PMID 28467729

N ENGL J MED . 2

JCO. VOLUME 35 • NUMBER 22 • AUGUST 1, 2017

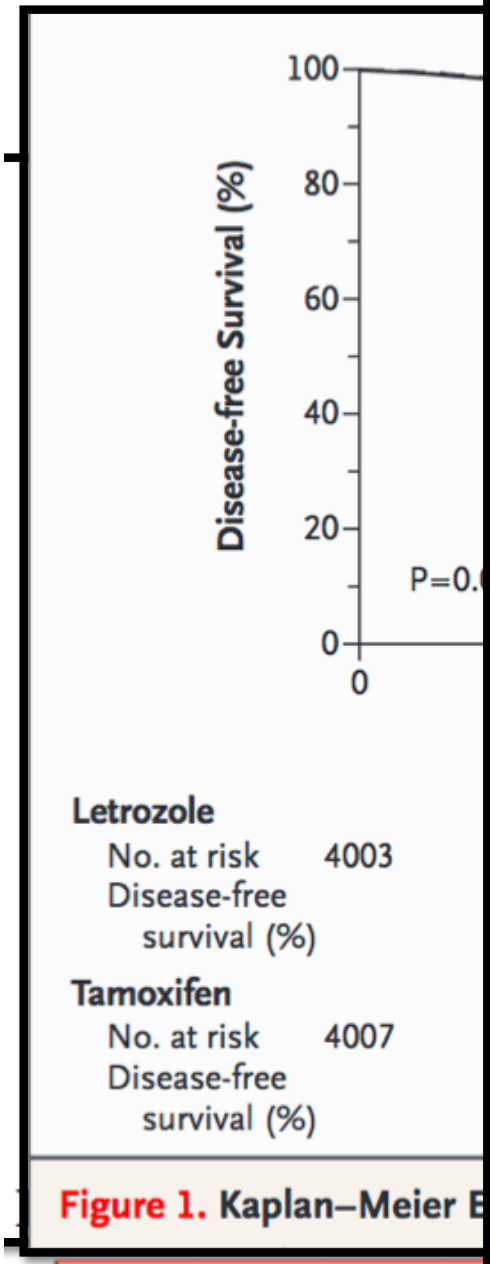


Figure 1. Kaplan–Meier E

N Engl J Med 2005
N Engl J Med 2009

Adjuvant AI in postmenopausal woman is superior to tamoxifen

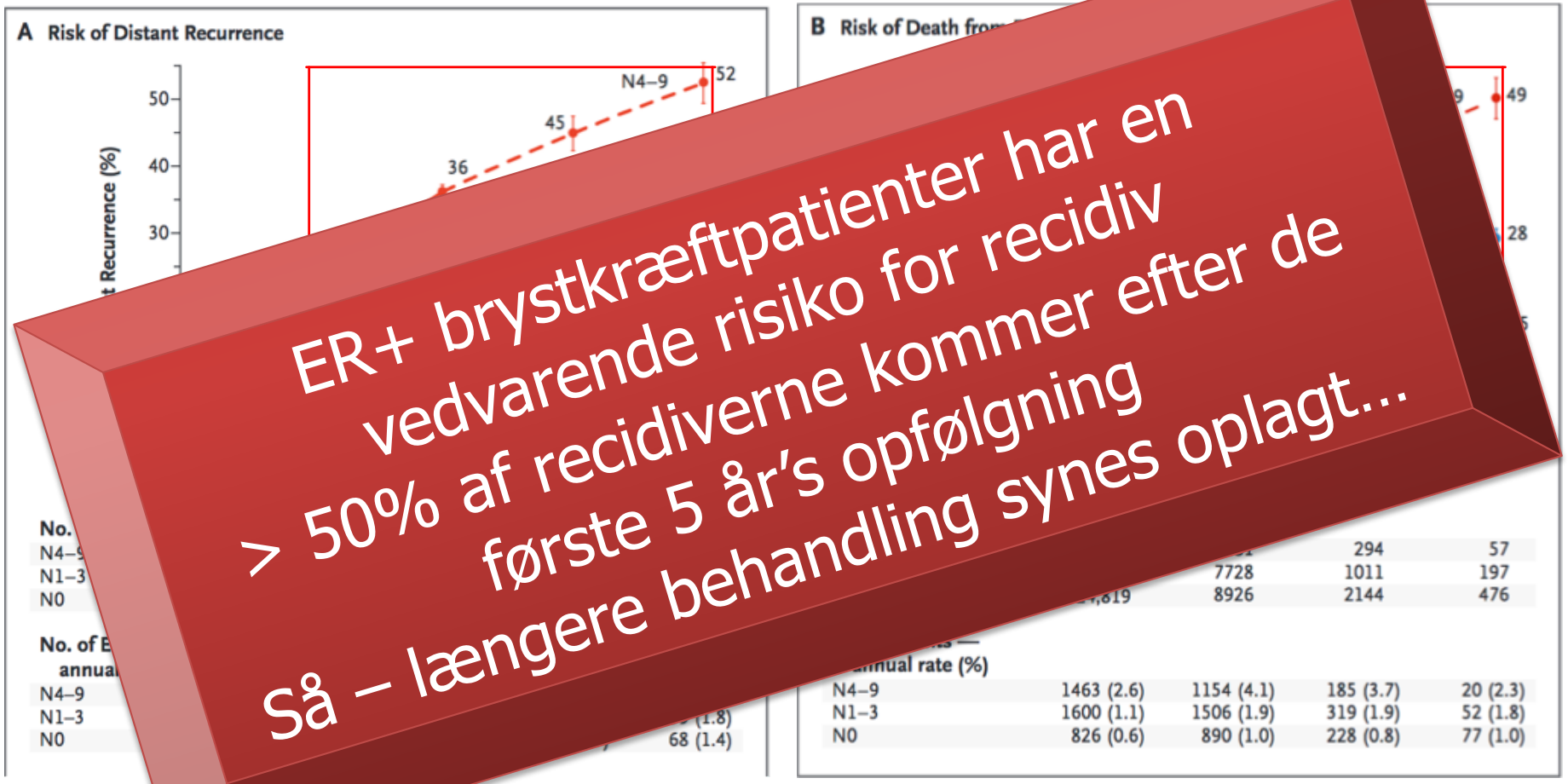
	5 years of tamoxifen *vs* none: EBCTCG previous meta-analysis[1] (n=10 645)		5 years of aromatase inhibitor *vs* 5 of tamoxifen: present meta-analys (n=34 882)		5 years of aromatase inhibitor *vs* none: estimated effects (product of two RRs†)	
	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
Breast cancer recurrence						
During years 0–4	0·53 (0·48–0·57)	2p<0·0001	0·70 (0·64–0·77)	2p<0·0001	0·37 (0·33–0·42)	2p<0·0001
During years 5–9	0·68 (0·60–0·78)	2p<0·0001	0·92 (0·83–1·01)	2p=0·082	0·63 (0·53–0·74)	2p<0·0001
Breast cancer mortality						
During years 0–4	0·71 (0·62–0·80)	2p<0·0001	0·79 (0·67–0·92)	2p=0·002	0·56 (0·46–0·68)	2p<0·0001
During years 5–9	0·66 (0·58–0·75)	2p=0·0001	0·91 (0·80–1·02)	2p=0·12	0·60 (0·50–0·72)	2p<0·0001

EBCTCG=Early Breast Cancer Trialists' Collaborative Group. RR=rate ratio. *Estimated from the aggregated data (apper
inhibitor *vs* none (RR_3) is obtained by direct multiplication of the rate ratio for 5 years of tamoxifen *vs* none (RR_1) by the rate ratio for 5 years of aromatase inhibitor *vs* 5 years of tamoxifen (RR_2) estimated from the aggregated data; 95% confidence limits for RR_3 are $\exp[(o-e)_1/v_1+(o-e)_2/v_2)-1{\cdot}96\sqrt{(1/v_1+1/v_2)}]$ and $\exp[(o-e)_1/v_1+(o-e)_2/v_2)+1{\cdot}96\sqrt{(1/v_1+1/v_2)}]$, respectively, where (o−e) and v are the observed minus expected statistics and their variances for the comparisons of 5 years of tamoxifen *vs* none and 5 years of aromatase inhibitor *vs* 5 years of tamoxifen (estimated from aggregated data from trials contributing to subtotal (a) in figure 4).

Table: **Estimation of the effect of 5 years of an aromatase inhibitor versus no endocrine treatment**

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Lancet 2015; 386: 1341–52

Risiko for fjern recidiv eller død af brystkræft gennem en 20 års periode

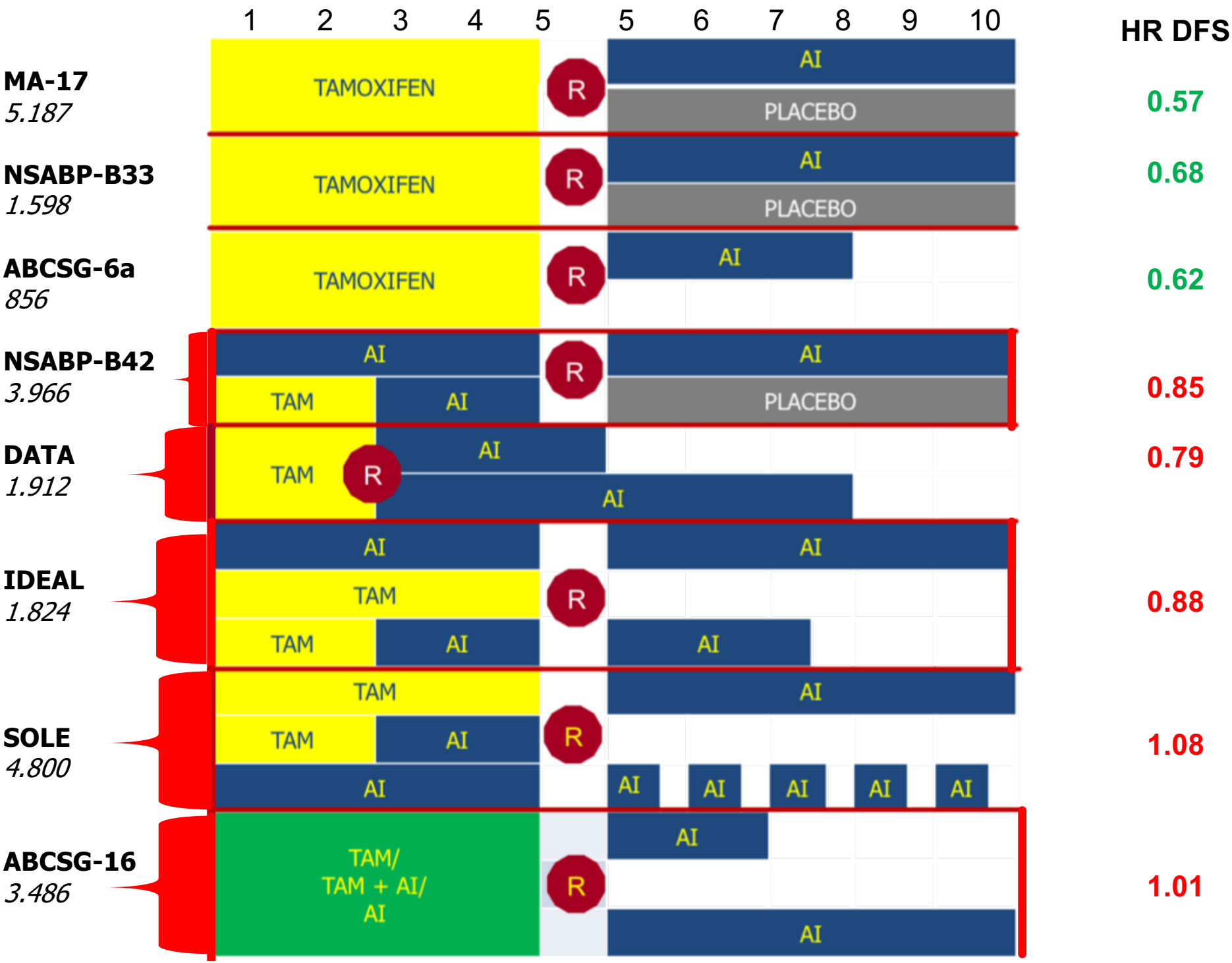


ER+ brystkræftpatienter har en vedvarende risiko for recidiv

> 50% af recidiverne kommer efter de første 5 år's opfølgning

Så – længere behandling synes oplagt...

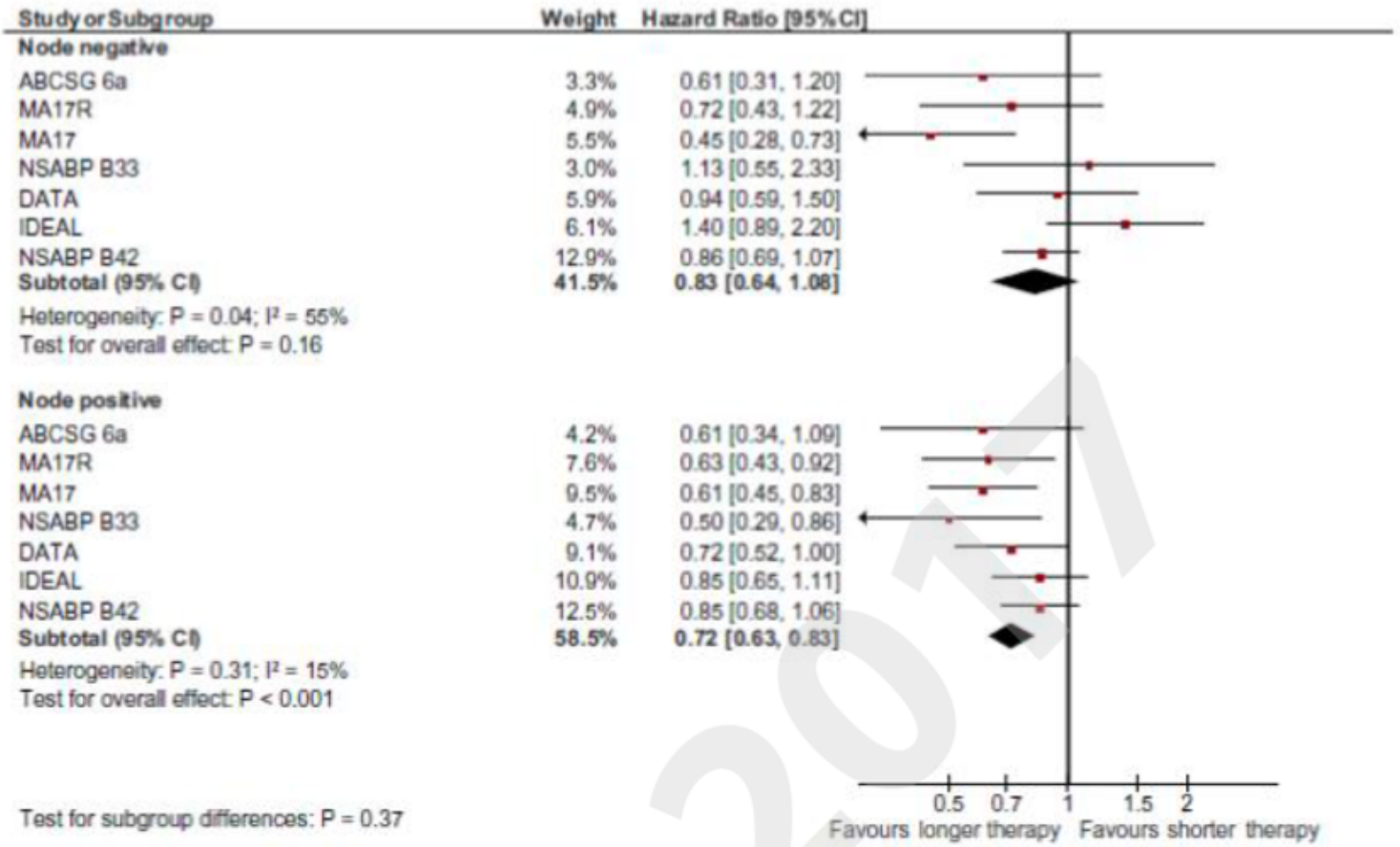
Pan H et al: NEJM 377;19 November 9, 2017


1 2 3 4 5 5 6 7 8 9 10
HR DFS
MA-17
5.187
TAMOXIFEN
R
AI
PLACEBO
0.57
NSABP-B33
1.598
TAMOXIFEN
R
AI
PLACEBO
0.68
ABCSG-6a
856
TAMOXIFEN
R
AI
0.62
NSABP-B42
3.966
AI
TAM
AI
R
AI
PLACEBO
0.85
DATA
1.912
TAM
R
AI
AI
0.79
IDEAL
1.824
AI
TAM
TAM
AI
R
AI
AI
0.88
SOLE
4.800
TAM
TAM
AI
AI
R
AI
AI AI AI AI AI
1.08
ABCSG-16
3.486
TAM/
TAM + AI/
AI
R
AI
AI
1.01

Meta-analysis

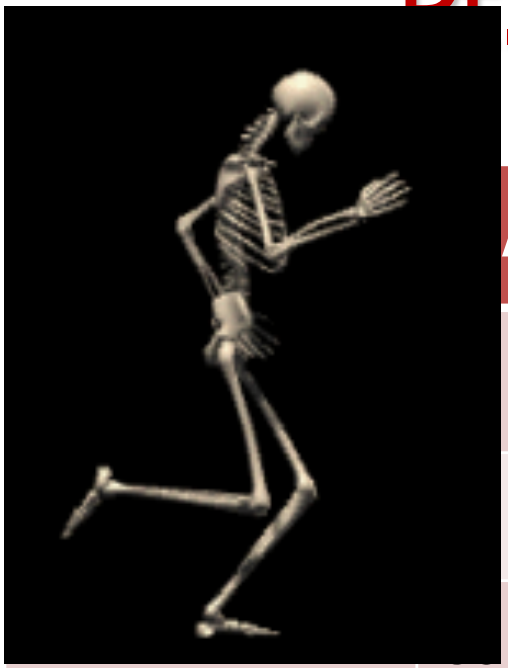
Meta-analysis: Extended AI Therapy

Forest Plot for Disease-free Survival According to Nodal involvement

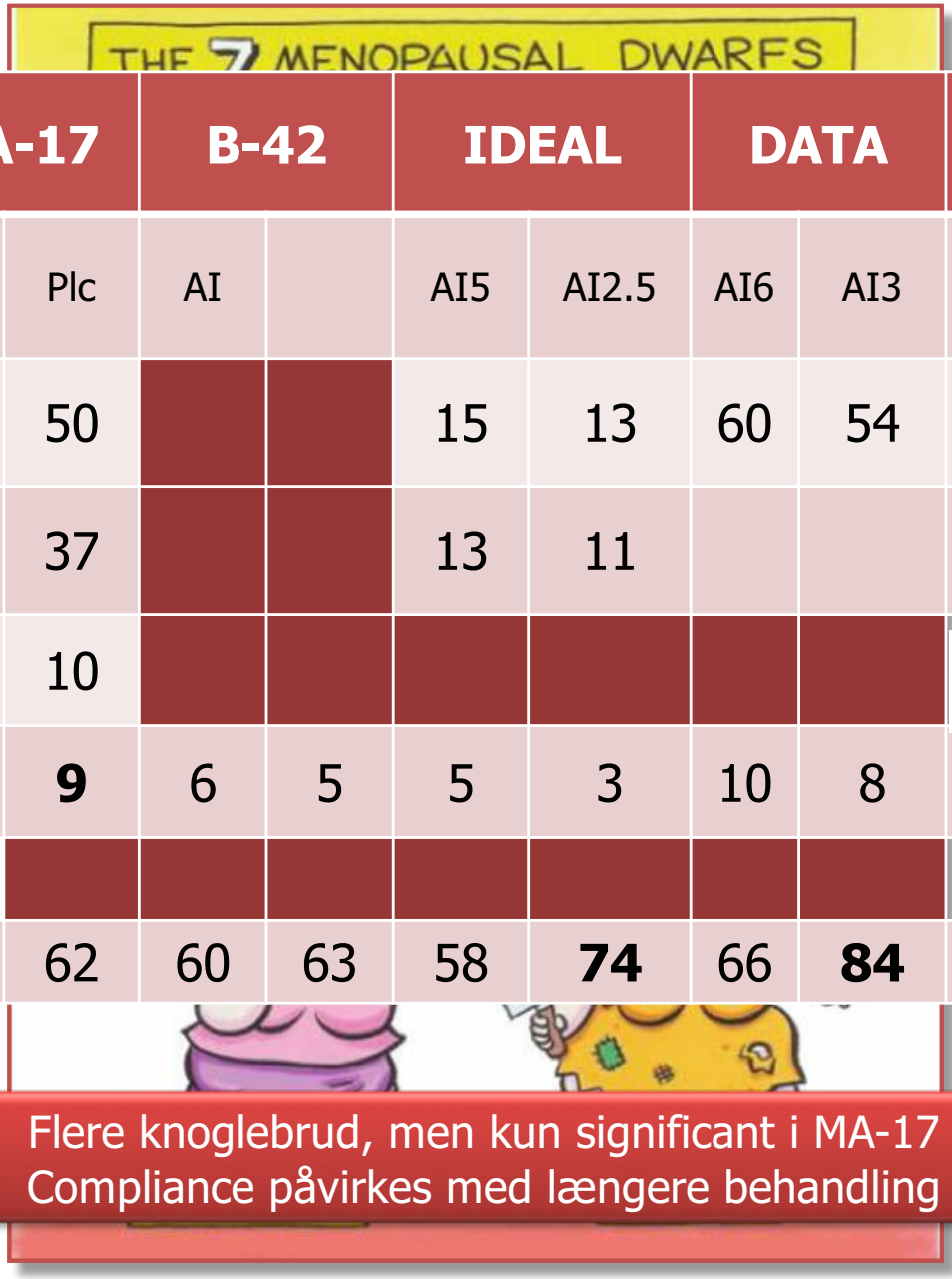


Goldvaser et al, *Cancer Treatment Reviews* 60 (2017) 53–59

Pt. oplevede bivirkninger



	MA-17		B-42		IDEAL		DATA		Sole		ABCSG-16	
		Plc	AI		AI5	AI2.5	AI6	AI3	AI cont	AI int	AI5	AI2
		50			15	13	60	54	68	66		
		37			13	11			54	52		
Tørre slimhinder	11	10										
Knoglebrud	**14**	**9**	6	5	5	3	10	8	10	9	6.3	4.7
Compliance	63	62	60	63	58	**74**	66	**84**	95	95	60	**80**

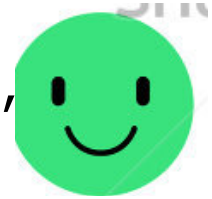


Flere knoglebrud, men kun significant i MA-17
Compliance påvirkes med længere behandling

Forlænget behandling med AI til postmenopausale patienter giver i gennemsnit:

AI efter initial tamoxifen

- Signifikant forbedret DFS efter 5 års tamoxifen (MA17, NSABP-B33, 6a)

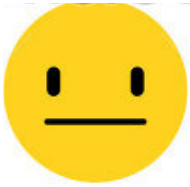


AI efter tidligere AI (2-5 år)

- Borderline/ingen gavn efter tidligere 2-5 års AI (MA17R, NSABP42, DA IDEAL

Pulsterapi med AI vs kont. AI

- Er hverken værre eller bedre (SOLE)



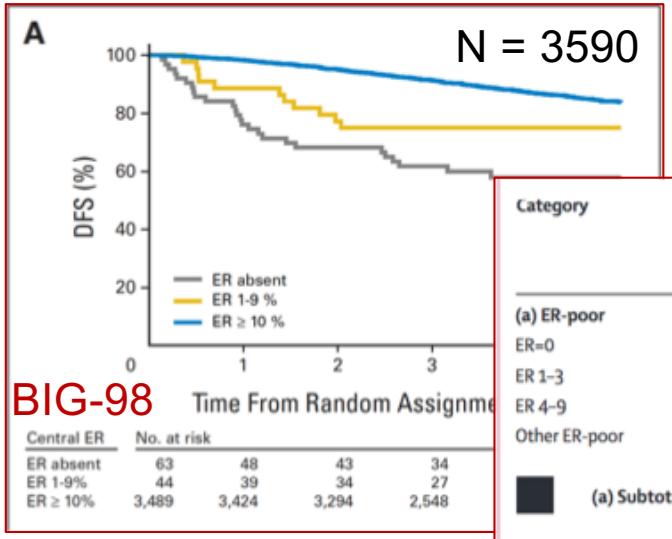
Ingen overlevelsesgevinst

EBCTCG is in 2018 conducting a meta-analysis regarding extended AI

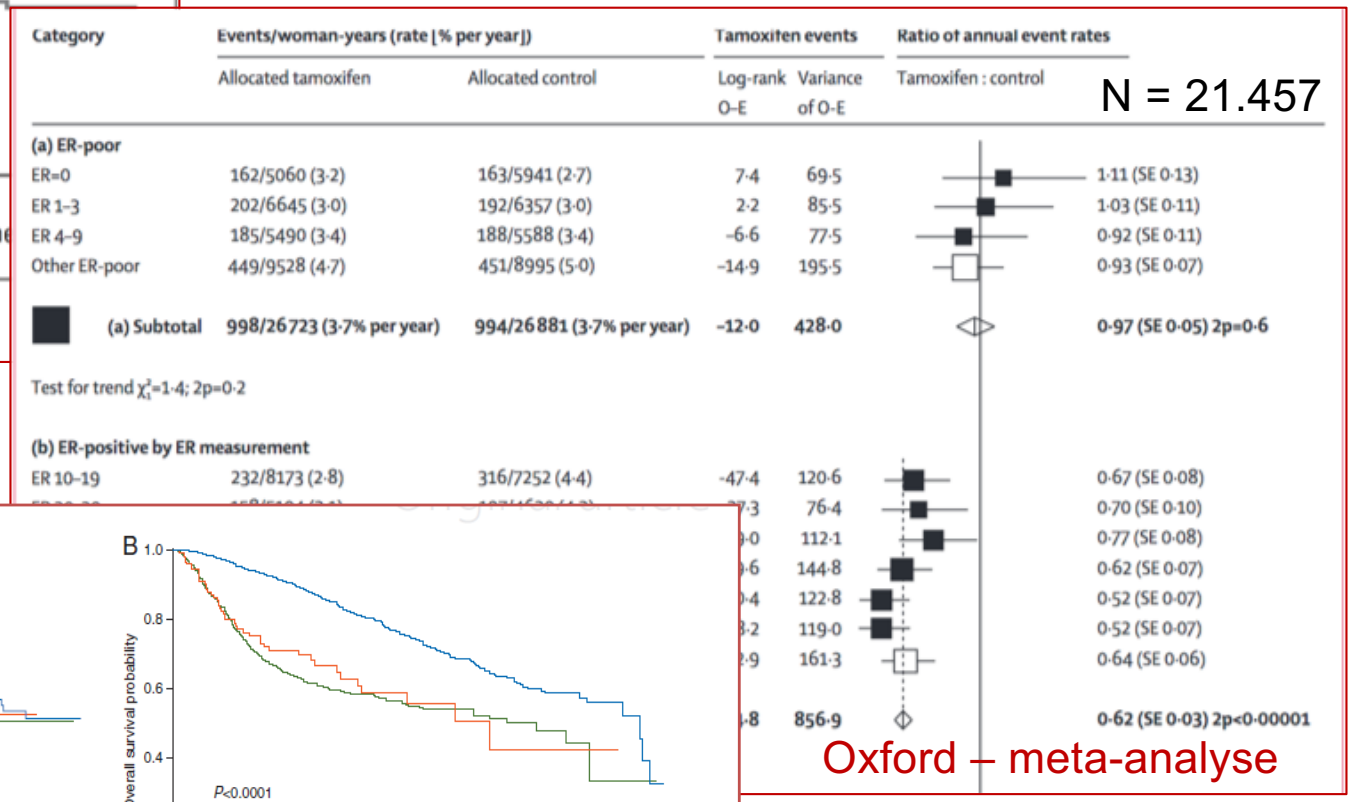
Pt selektion til forlænget behandling?

- Pt relaterede faktorer incl. knogle sundhed
- STEEP "**composite**" risiko rater/Q-score
- ER-status
  - ASCO guidelines: ER+ if > 1%
- Genomic Subtype (sene recidiver) + ex Q-score
  - Ann Oncol. 2014; 25: 339-345 PAM50
  - Ann Oncol. 2015; 26: 1685-1691 PAM50
  - J Clin Oncol 2015 Mar 10;33(8) PAM50
  - J Clin Oncol 2016;34:2350–8 OncotypeDX
  - J Clin Oncol 2018;57 DBCG – In press

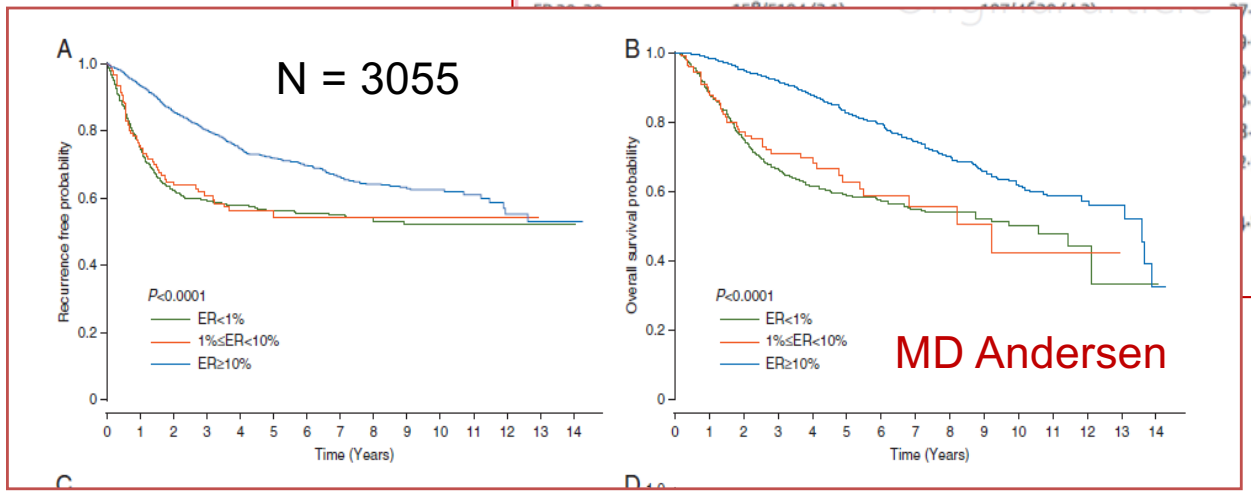
ERpos?



BIG-98



Oxford – meta-analyse



MD Andersen

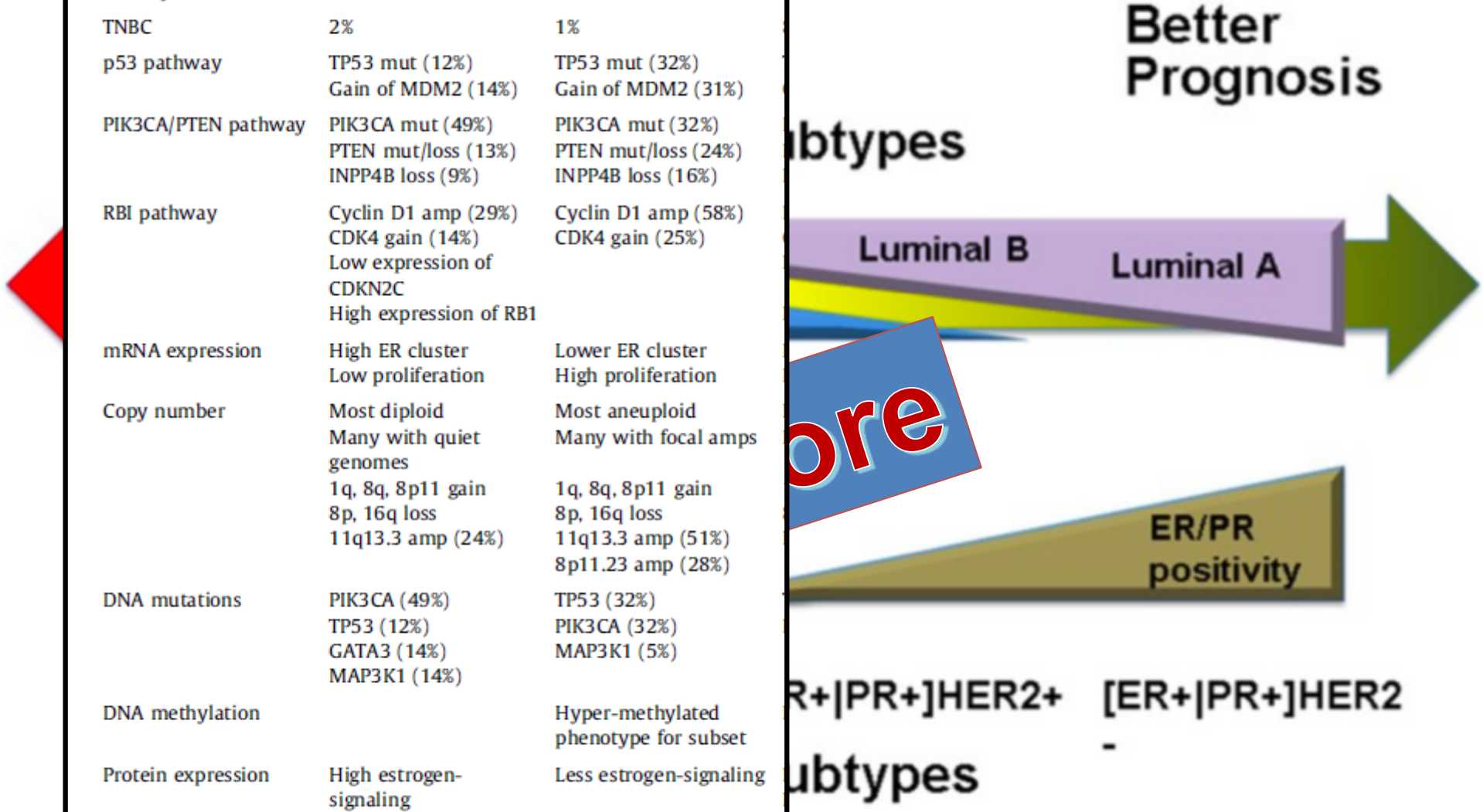
JCO, Vol 25, 25 2007, Lancet, Vol 378 August 27, 2011. Annals of Oncology Vol 28 2017

St. Gallen
Ann Oncol 2005; 16: 1569–1583
Ann Oncol 2009; 20: 1319–1329
Ann Oncol 2015; 26: 1533–1546.

per i komb. med
ivermutationer ?

Table 1
Summary of disease subtype findings highlighting some of the dominant genom

	Luminal A	Luminal B
ER-positive/HER2-negative	87%	82%
HER2-positive	7%	15%
TNBC	2%	1%
p53 pathway	TP53 mut (12%) Gain of MDM2 (14%)	TP53 mut (32%) Gain of MDM2 (31%)
PIK3CA/PTEN pathway	PIK3CA mut (49%) PTEN mut/loss (13%) INPP4B loss (9%)	PIK3CA mut (32%) PTEN mut/loss (24%) INPP4B loss (16%)
RBI pathway	Cyclin D1 amp (29%) CDK4 gain (14%) Low expression of CDKN2C High expression of RB1	Cyclin D1 amp (58%) CDK4 gain (25%)
mRNA expression	High ER cluster Low proliferation	Lower ER cluster High proliferation
Copy number	Most diploid Many with quiet genomes 1q, 8q, 8p11 gain 8p, 16q loss 11q13.3 amp (24%)	Most aneuploid Many with focal amps 1q, 8q, 8p11 gain 8p, 16q loss 11q13.3 amp (51%) 8p11.23 amp (28%)
DNA mutations	PIK3CA (49%) TP53 (12%) GATA3 (14%) MAP3K1 (14%)	TP53 (32%) PIK3CA (32%) MAP3K1 (5%)
DNA methylation		Hyper-methylated phenotype for subset
Protein expression	High estrogen-signaling High cMYB RPPA reactive subtypes	Less estrogen-signaling High FOXM1 and cMYC RPPA reactive subtypes



Cancer Treatment Reviews 59 (2017) 22–32

Endokrin behandling – efter 2018

- Behandling gavner IKKE – hvis den ikke tages.
  Pt. undervisning, akupunktur, motion mv
- Undgå anbefaling – ”for en sikkerhede skyld”
- Finde de ”rigtige patient kategorier”, så effekt overføres til overlevelse
  - Flere samarbejdede algoritmeværktøjer – stadie, alder, patologi, molekylærer subtyper, driver mutationer mv
- Andre veje – end bare længere og mere behandling.
  - CDk4/6 inhibitorer, Check-point-inhibitorer

Endokrin behandling - forskning

- Påvisning af markører, der har betydning for
  - Primær resistens: PÅ PRIMÆR tumor
    - Aurora kinase A, TILs?
  - Sekundær resistens: På ctDNA efter ex. 3 års endokrin behandling?
    - ESR1mut. (En konsekvens af AI behandling?)

Patienten ønsker:
Den rette behandling fra start

Lægen ønsker:
Effektiv behandling uden alvorlige bivirkninger

DBCG 40

Hvis dette ikke hjælper, kan De komme igen – så skal De få noget andet.
Kunne jeg så ikke ligesågodt få det andet med det samme!

Storm P

Strategi 2018

	ÅR 0	År 2 ½			5 år		
						PRÆ N+	TAM 5 år
			PRÆ	TAM 2½ år	#	PRÆ N-	stop
PRÆ > 35 år§	TAM 2½ år	#				POST	2 AI
			POST	AI 5 år			
POST	AI 5 år + zoledronsyre						

ERpos >10%?

test status
§ præ < 35 år, højrisiko, OFS + TAM/AI