

Endokrin behandling

Udvikling gennem 30+ år

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Historisk perspektiv

- ❑ 1896 Beatson – ooforektomi
 - ❑ Østrogen binder til østrogen receptor ($ER\alpha$ og $ER\beta$) som er transkriptionsaktivatorer
 - ❑ Godt 70% af mammatumorer ER-positive
 - ❑ Endokrin behandling inducerer respons hos ca. 50%
 - ❑ Ved endokrin responsiv sygdom inducerer 2. Og følgende linier endokrin behandling respons hos 20-40%
-

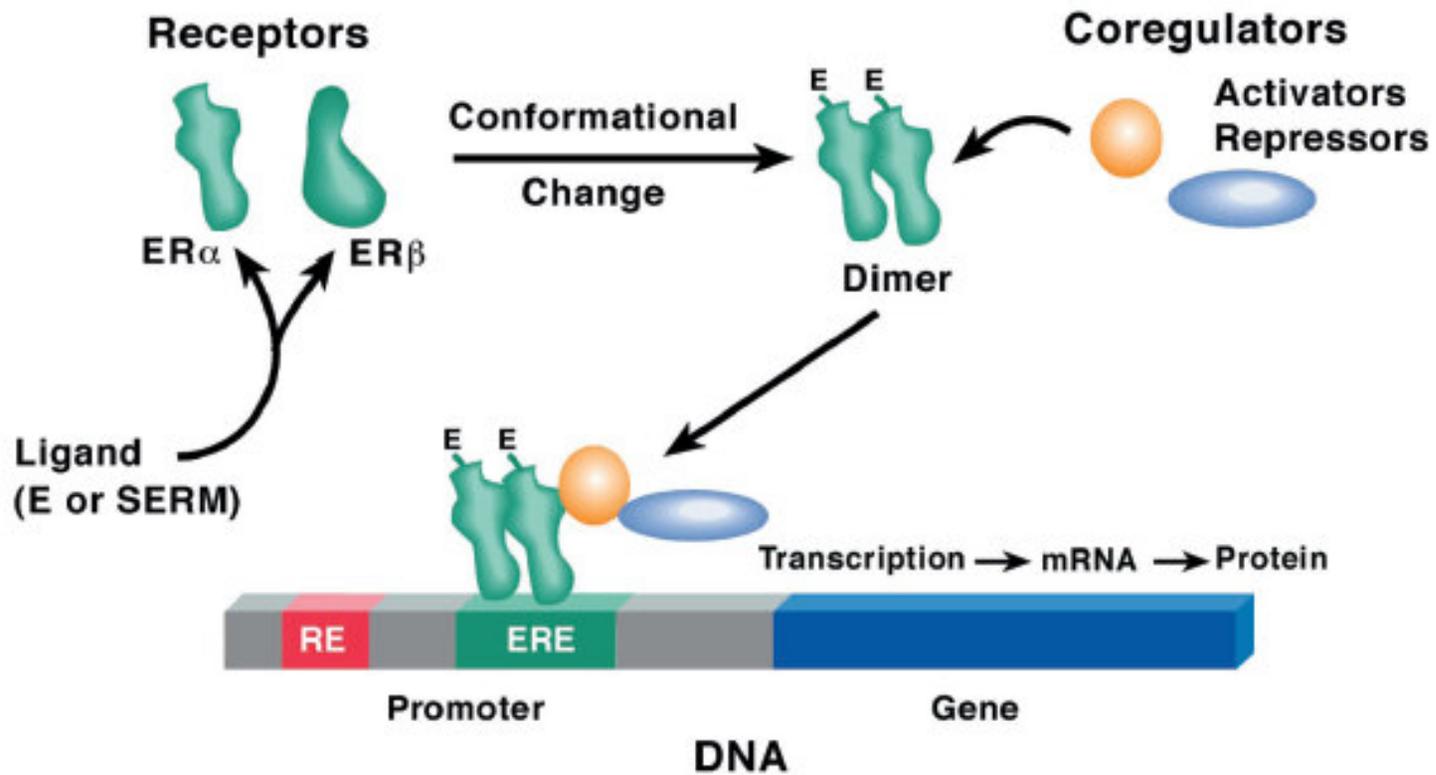


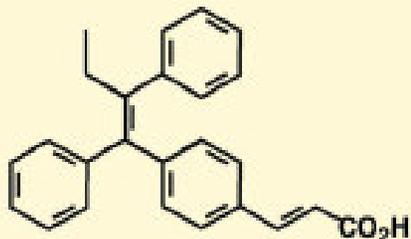
Fig 3. Mechanism of gene transactivation by ER.

Endokrine behandlinger

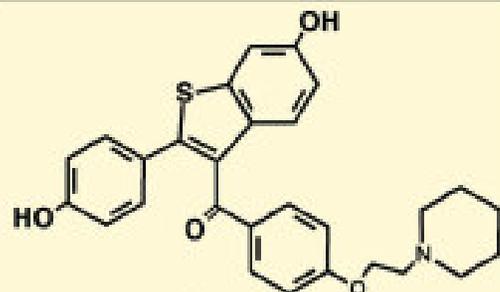
	Virkning	Eksempel
Steroid hormoner		Østrogener Gestagener Androgener Corticosteroider
SERM	Hæmmer østrogen-receptoren	Tamoxifen
Aromatase Inhibitorer	Hæmmer østrogensyntesen	Anastrozol Letrozol Exemestan
SERD	Nedregulerer østrogen receptoren	Fulvestrant
Ovariel Suppression	Ophæver ovariel østrogen produktion	Ooforektomi, LHRH agonister

Adjuvant behandling

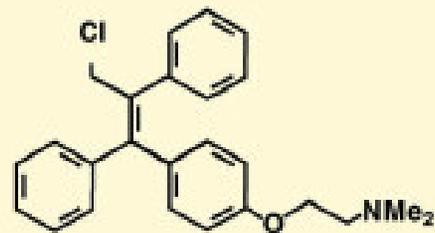
- Tamoxifen standard indtil 2004
 - Aromatase-inhibitorer alene eller i kombination standard 2005
-



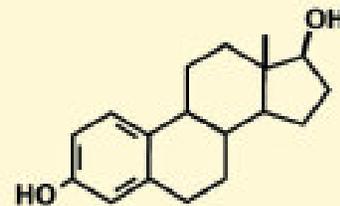
GW 5638
(triphenylethylene)



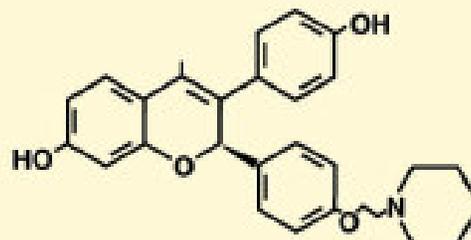
raloxifene
(benzothiophene)



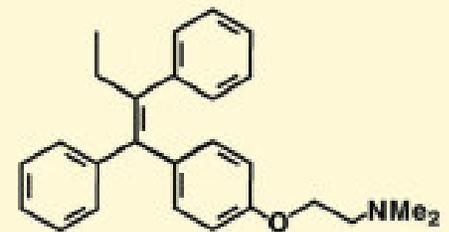
toremifene
(triphenylethylene)



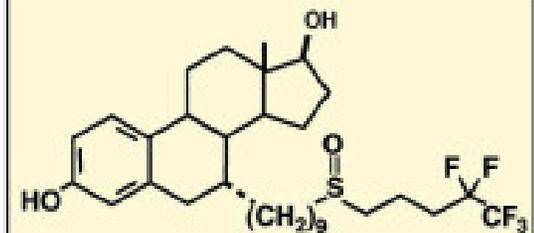
estradiol



EM-652
(benzopyran)



tamoxifen
(triphenylethylene)

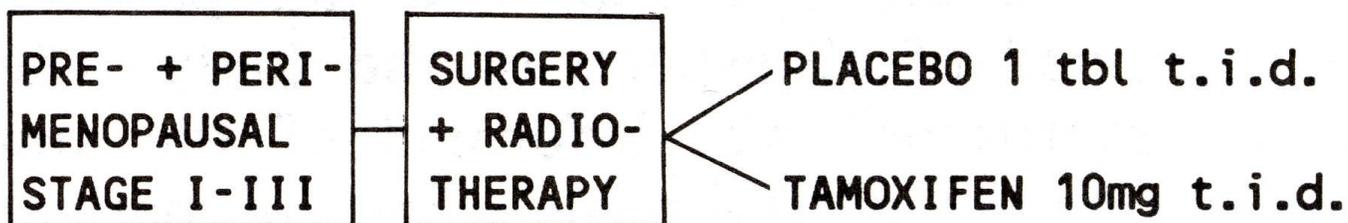


ICI 182780
(steroid)

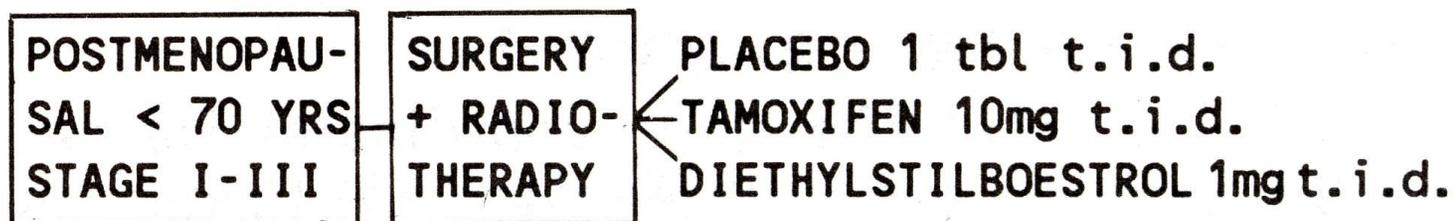
In the beginning:

The Copenhagen breast cancer trials 1975-1987
Palshof, Mouridsen og Dæhmfeldt

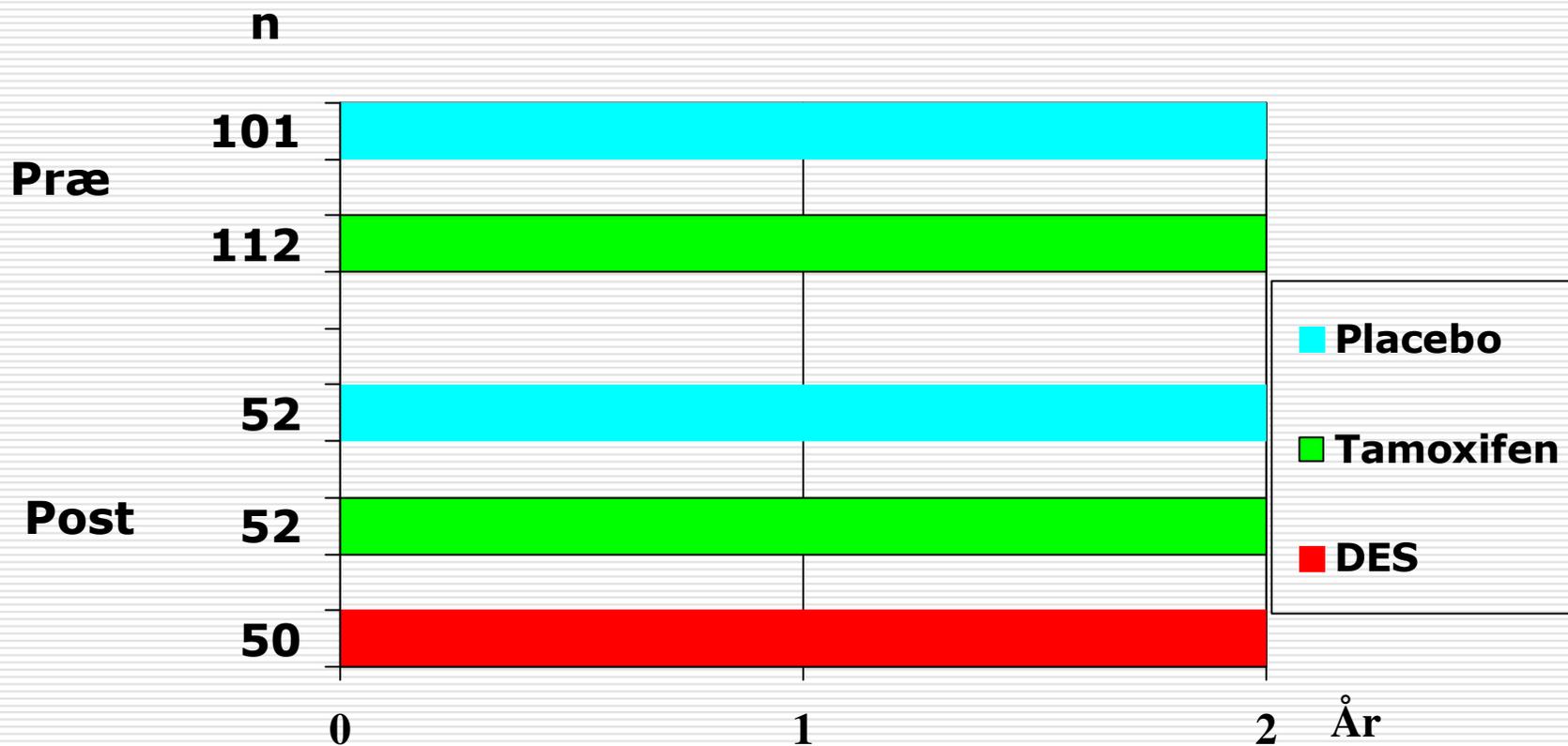
PREMENOPAUSAL TRIAL:



POSTMENOPAUSAL TRIAL:



Copenhagen Trials



Copenhagen Trials

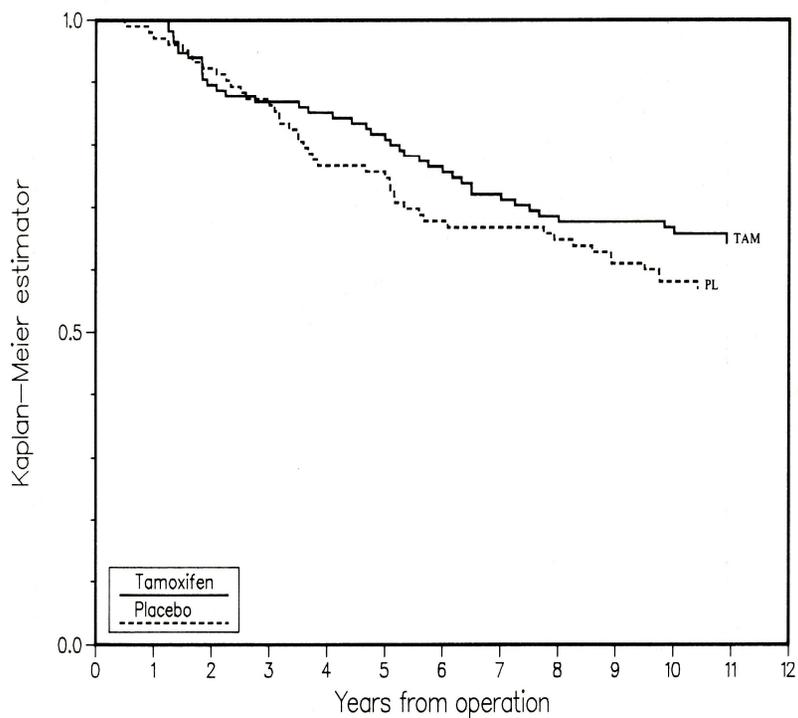


Figure 8-2a.
Overall survival in premenopausal patients.

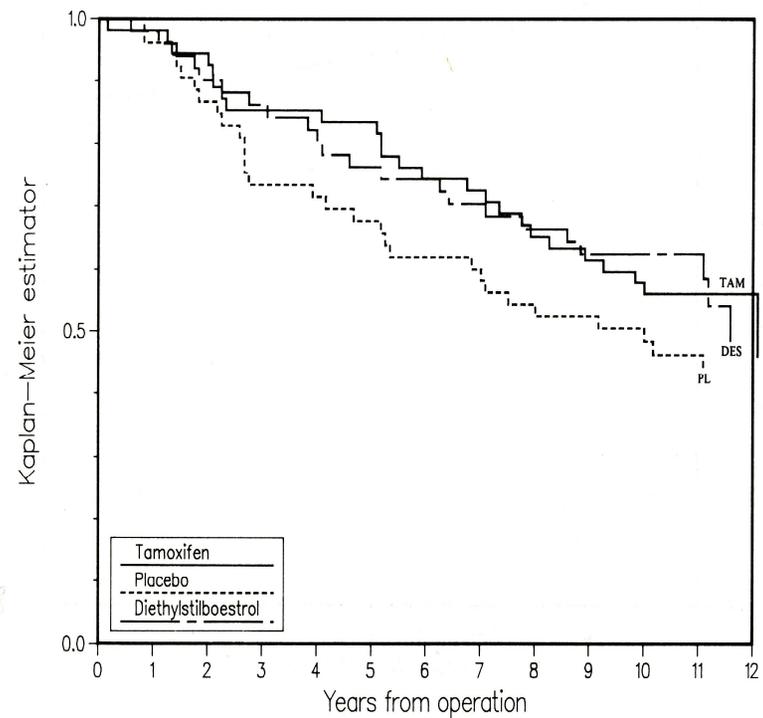
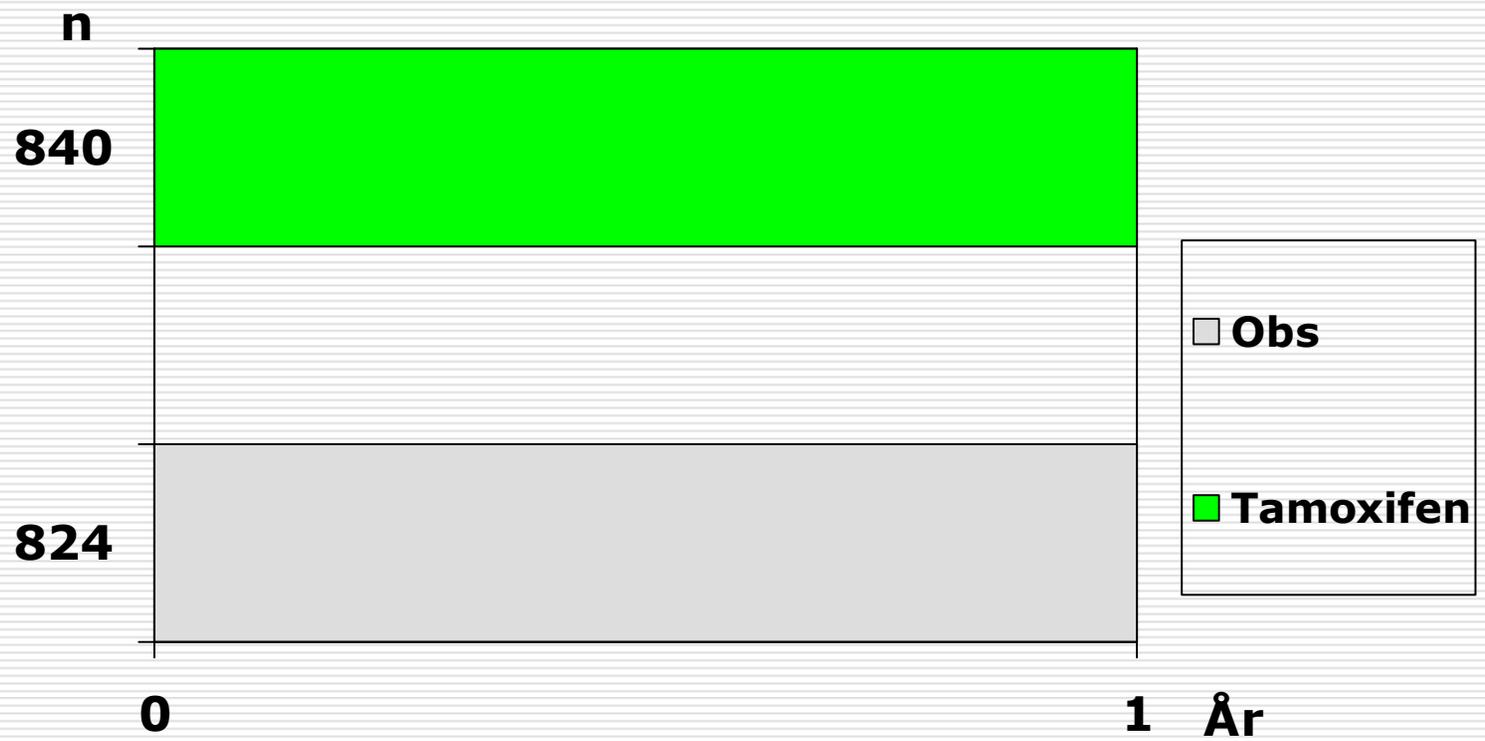


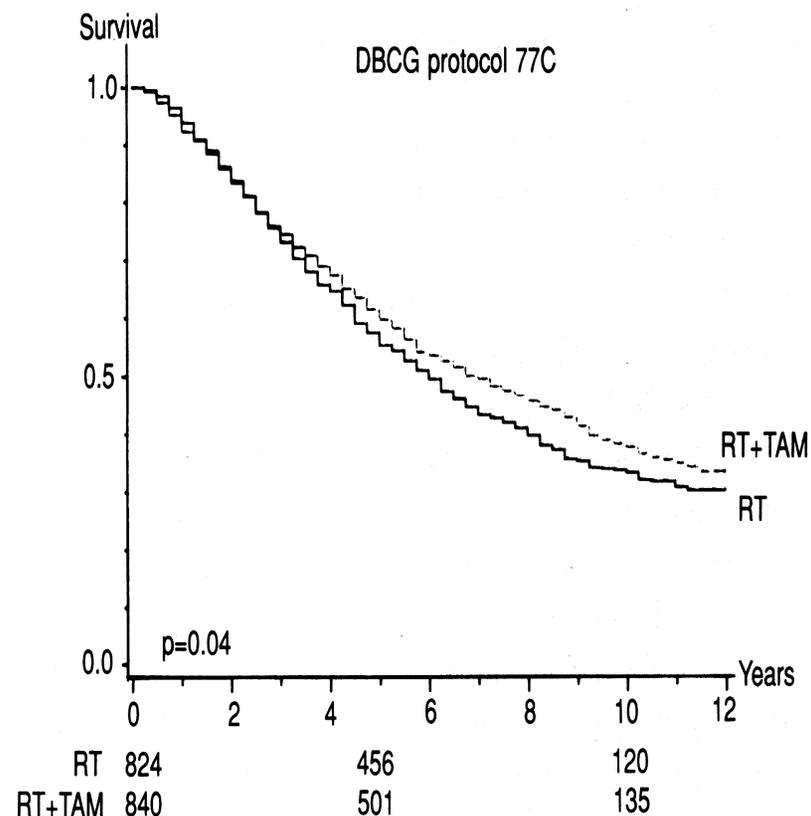
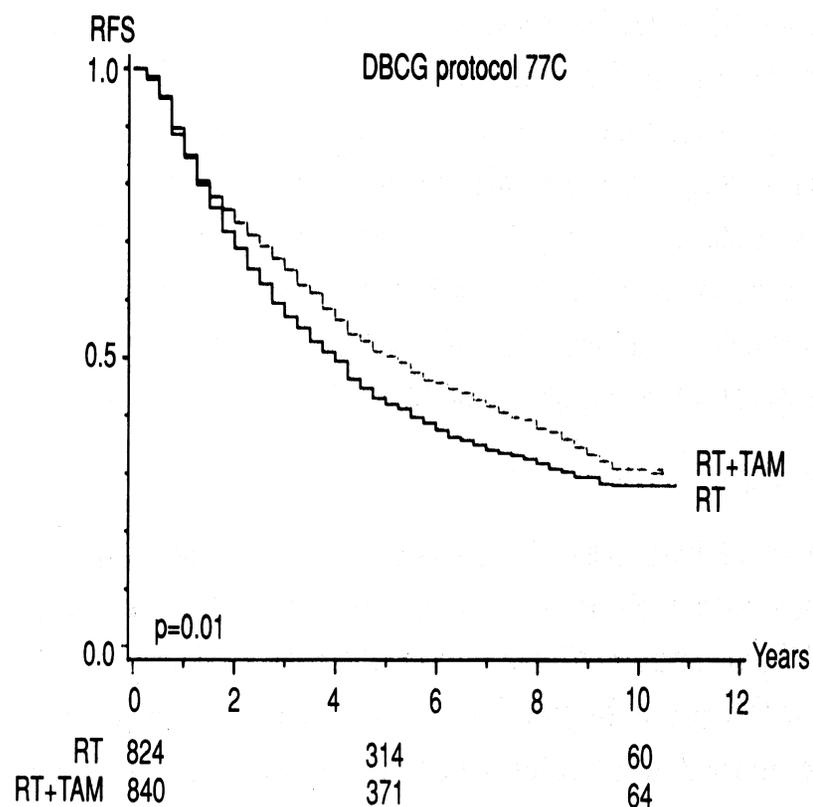
Figure 8-4a.
Overall survival in postmenopausal patients.

DBC 77c

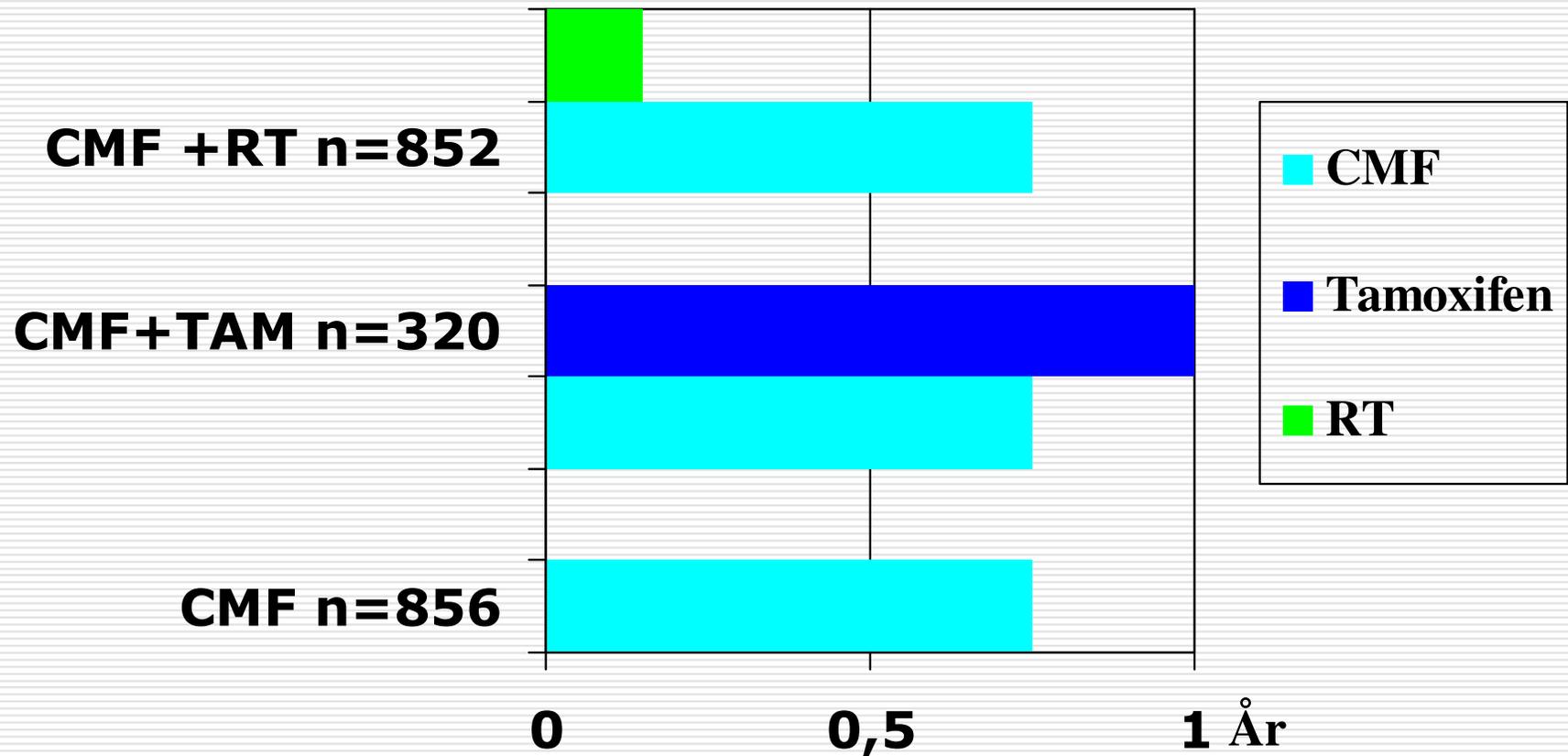


DBCG 77c

Rose et al

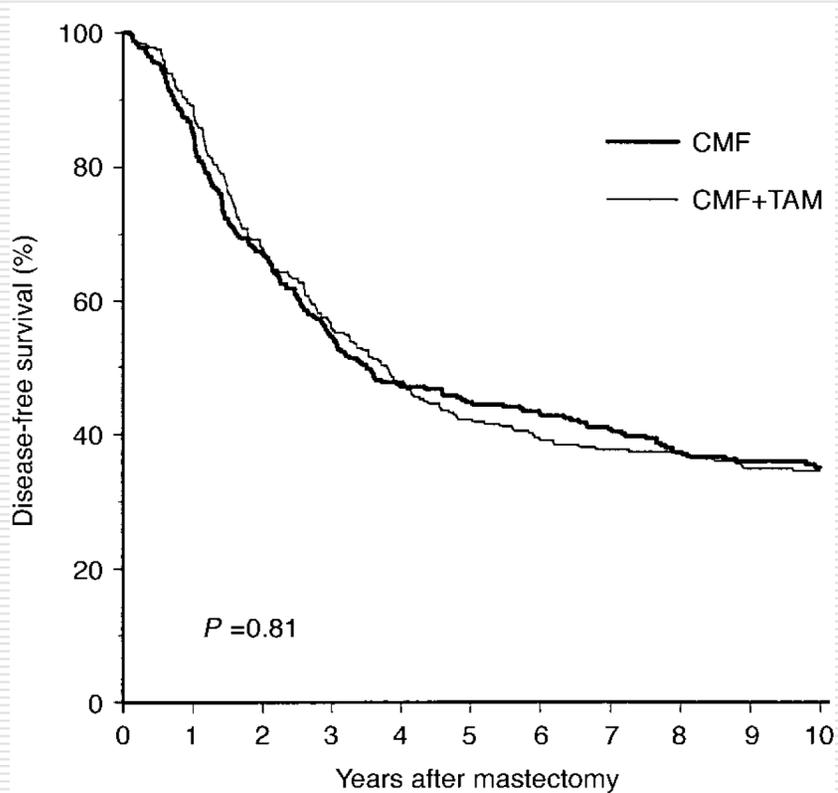


DBCG 82c

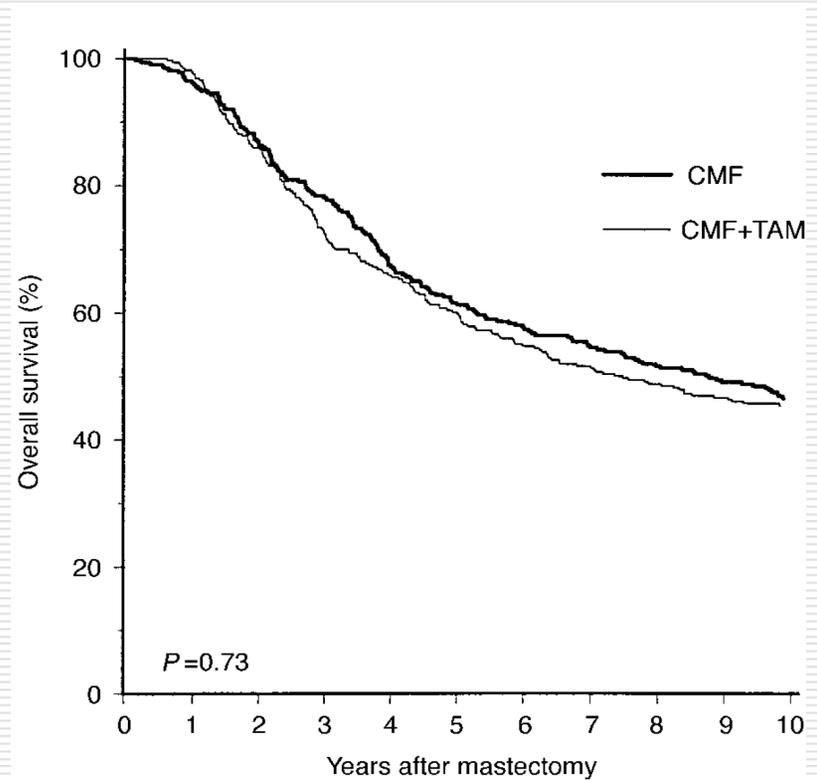


DBCG 82c

Andersson et al



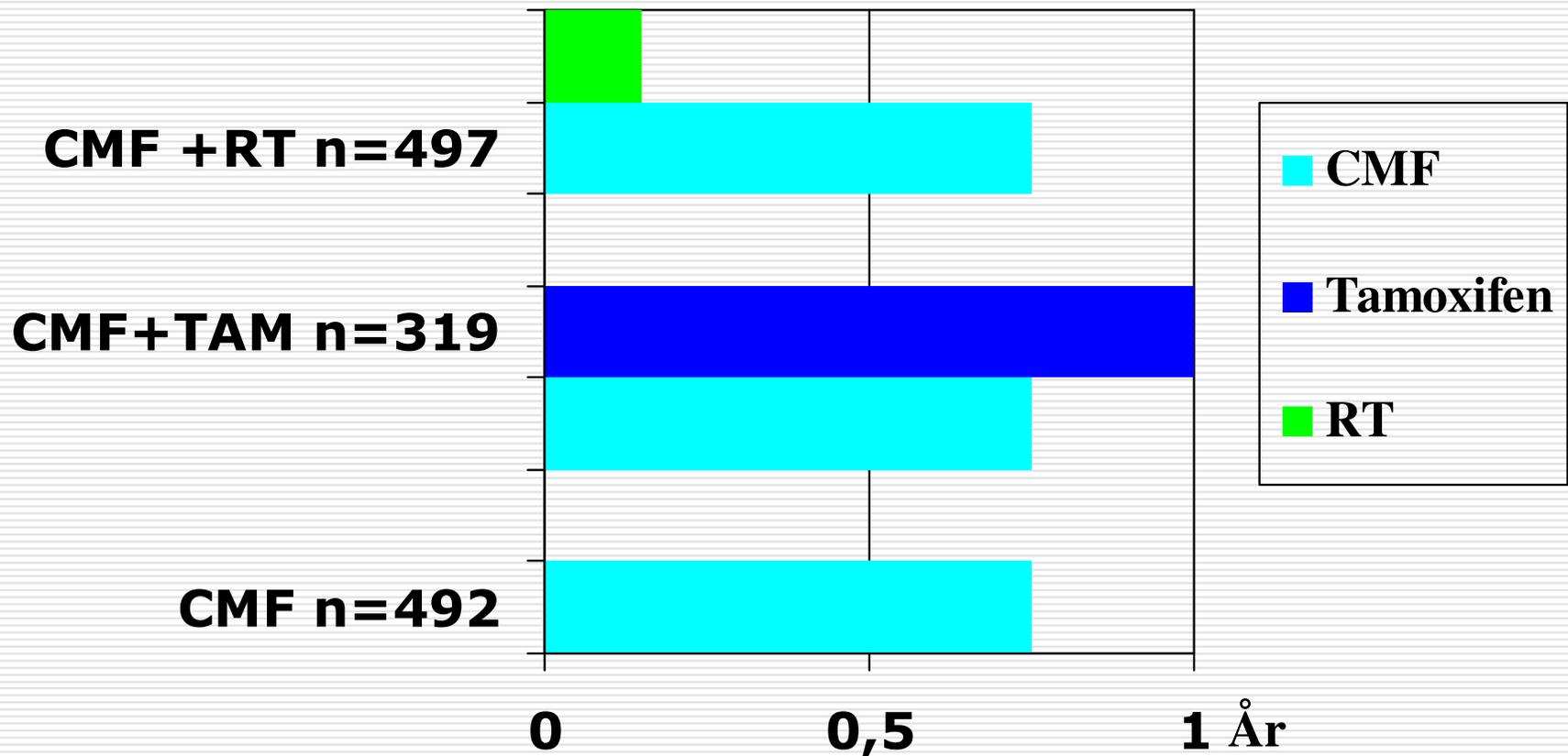
CMF	314	204	142	128	110	62
CMF+TAM	320	206	143	114	107	57



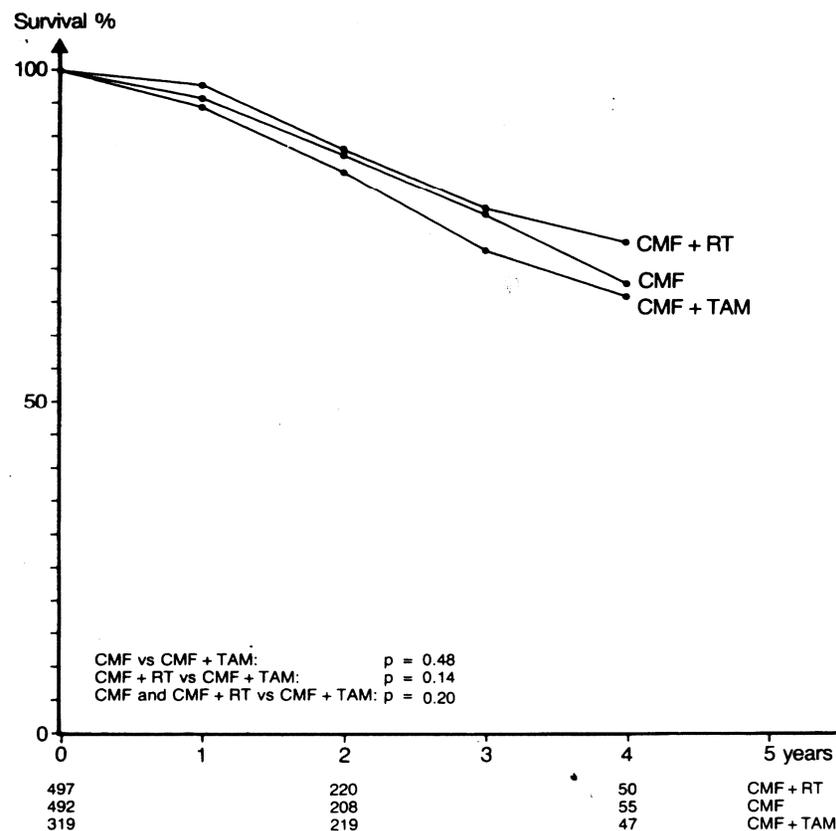
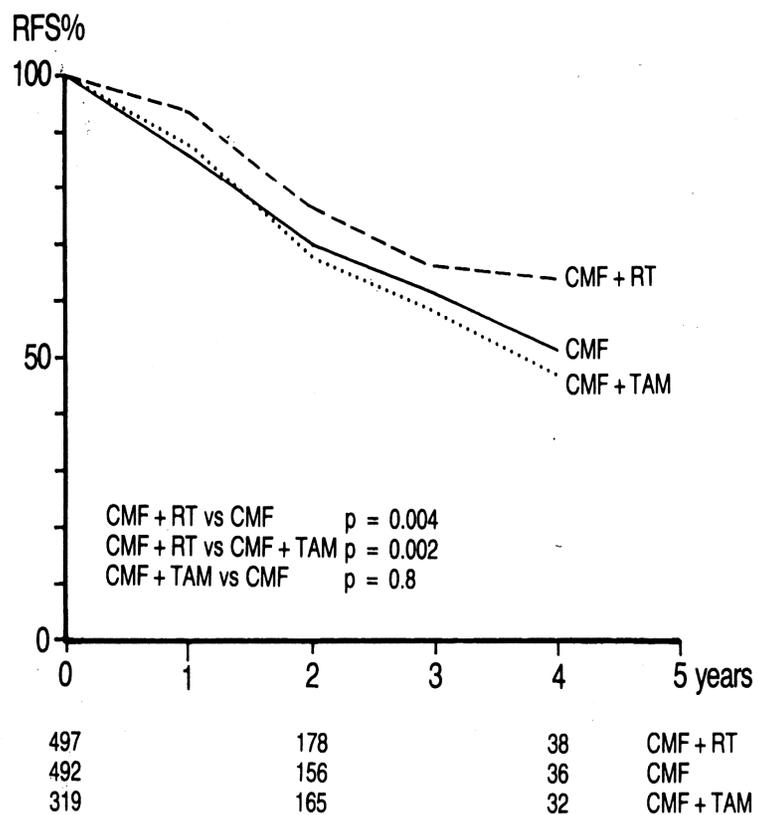
CMF	314	271	211	180	162	146
CMF+TAM	320	274	211	175	156	145

DBCG 82b

Dobernowsky et al



DBCG 82b

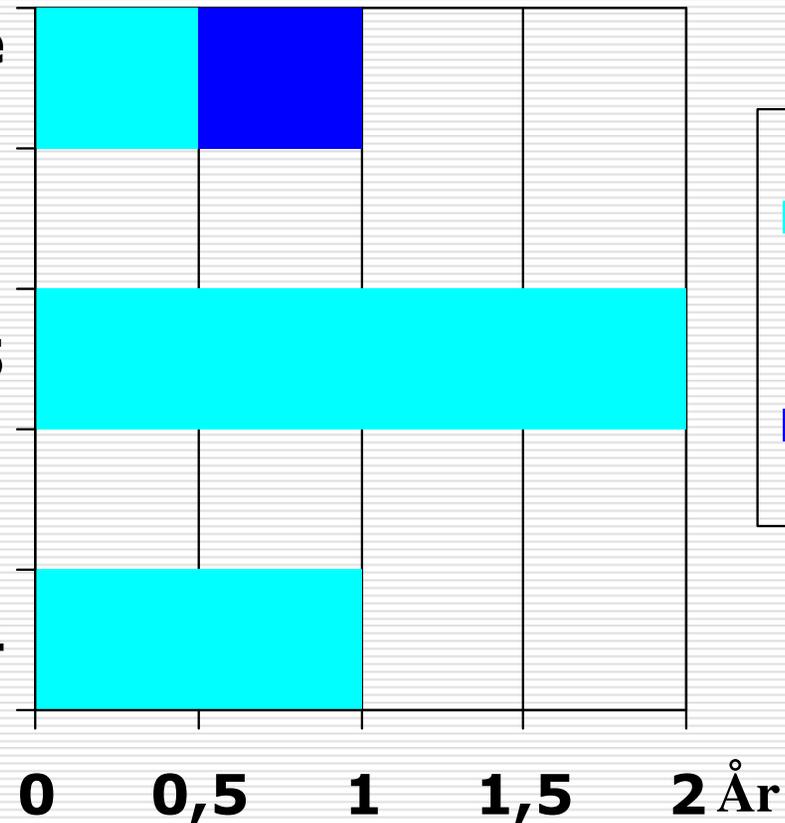


DBCG 89c

Tamoxifen+megace
n=526

Tamoxifen n=535

Tamoxifen n=554



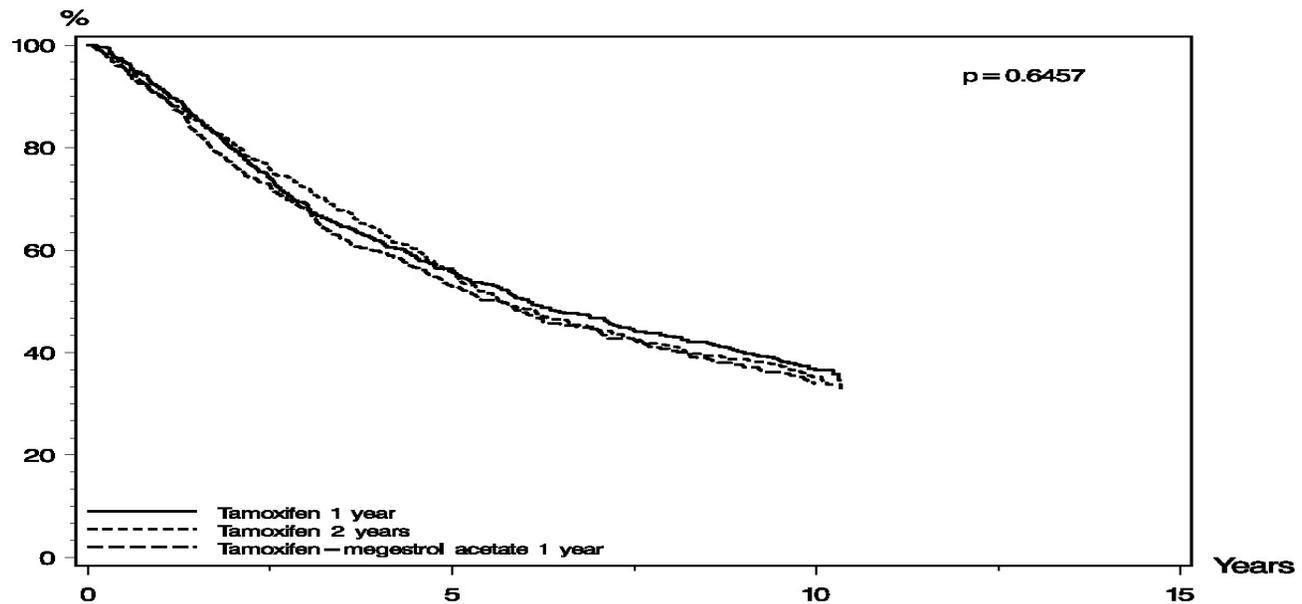
Tamoxifen

Megace

DBCG 89c

Andersen et al

Disease-free Survival, ITT population



No. at risk:

Tamoxifen 1 year

554

327

205

1

0

Tamoxifen 2 years

535

330

196

5

0

Tamoxifen-megestrol acetate 1 year

526

294

195

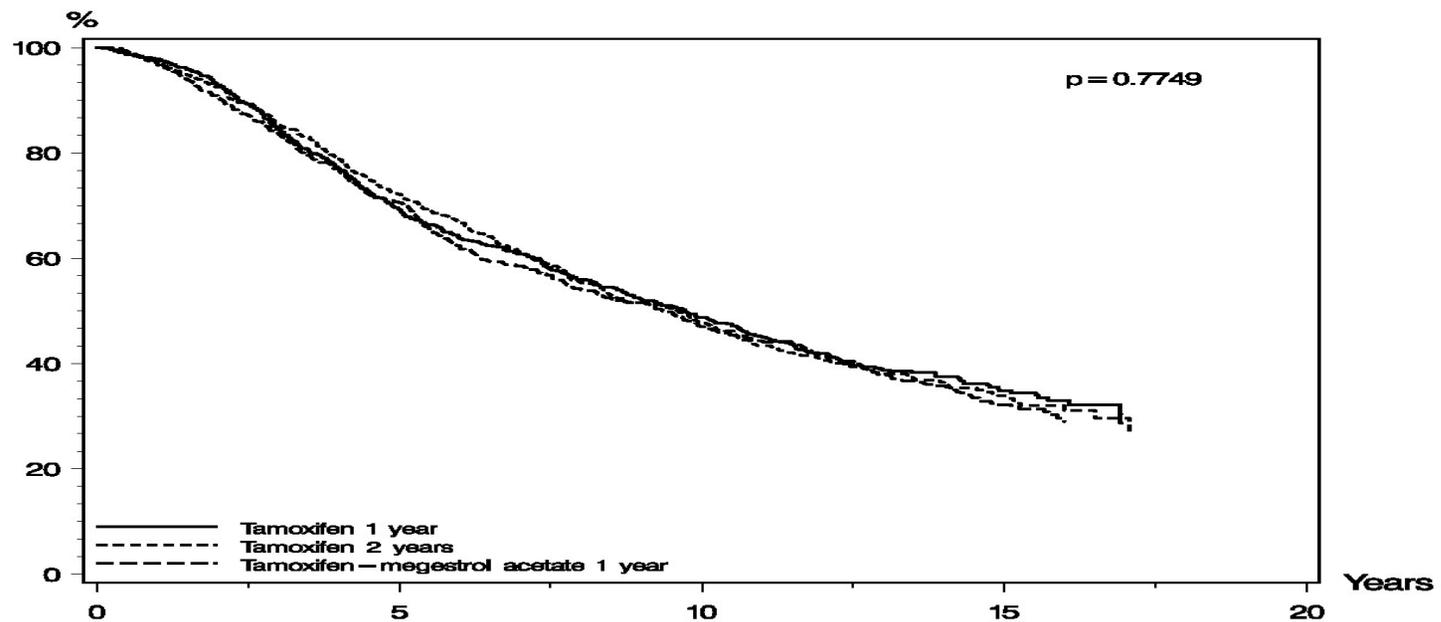
1

0

DBCG 89c

Andersen et al

Overall Survival, ITT population



No. at risk:	0	5	10	15	20
Tamoxifen 1 year	554	384	270	95	0
Tamoxifen 2 years	535	386	256	80	0
Tamoxifen + megestrol acetate 1 year	526	371	247	85	0

Verden stod ikke stille



The NEW ENGLAND
JOURNAL of MEDICINE

Volume 319:1681-1692

December 29, 1988

Number 26

Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. Early Breast Cancer Trialists' Collaborative Group

Adjuverende tamoxifen

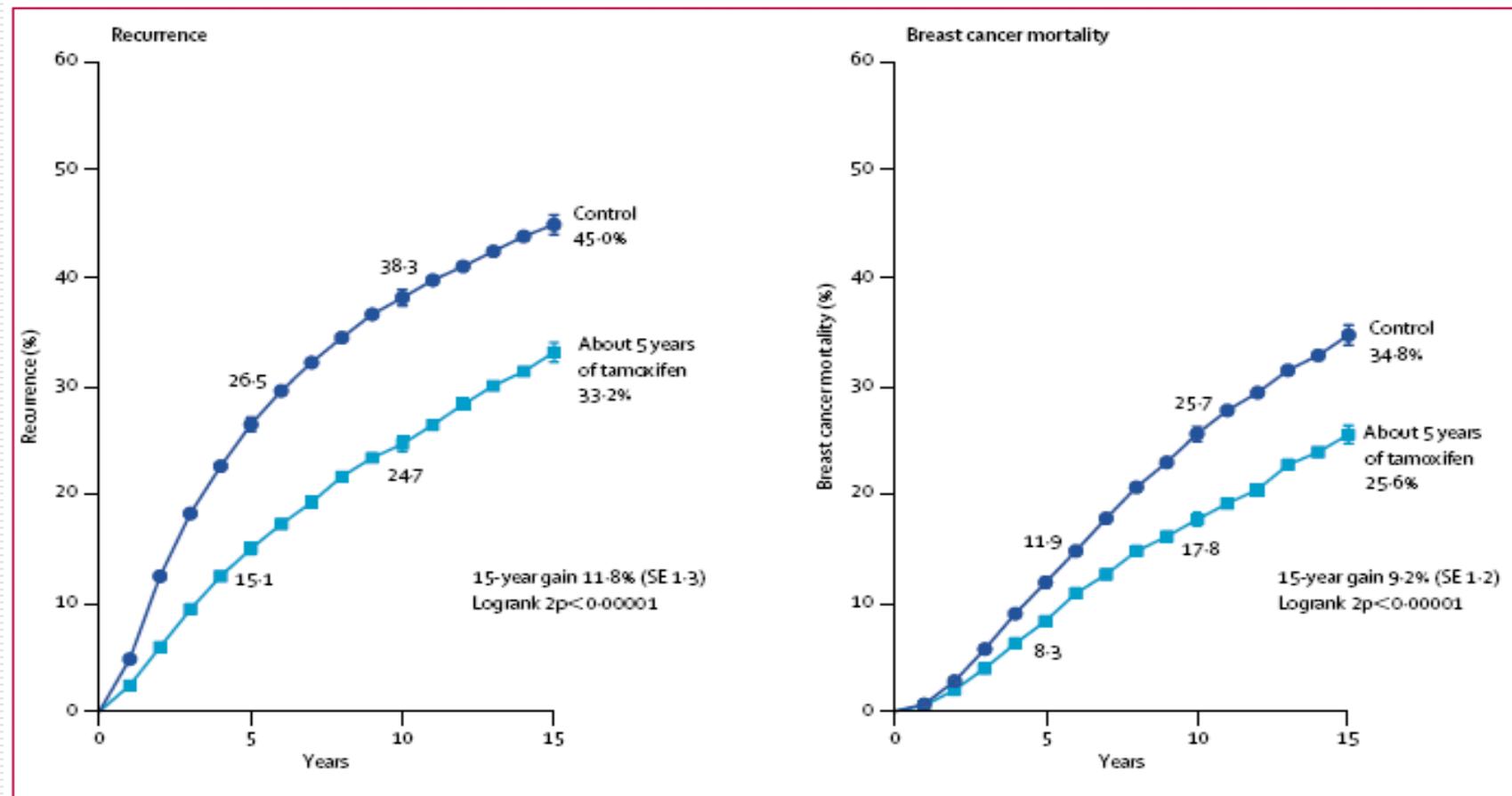


Figure 8: About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality
 10 386 women: 20% ER-unknown, 30% node-positive. Error bars are $\pm 1SE$.

Adjuverende tamoxifen

Effekt på dødelighed vs. alder

(c) Entry age (trend $\chi^2_1=0.4$; $2p>0.1$; NS)

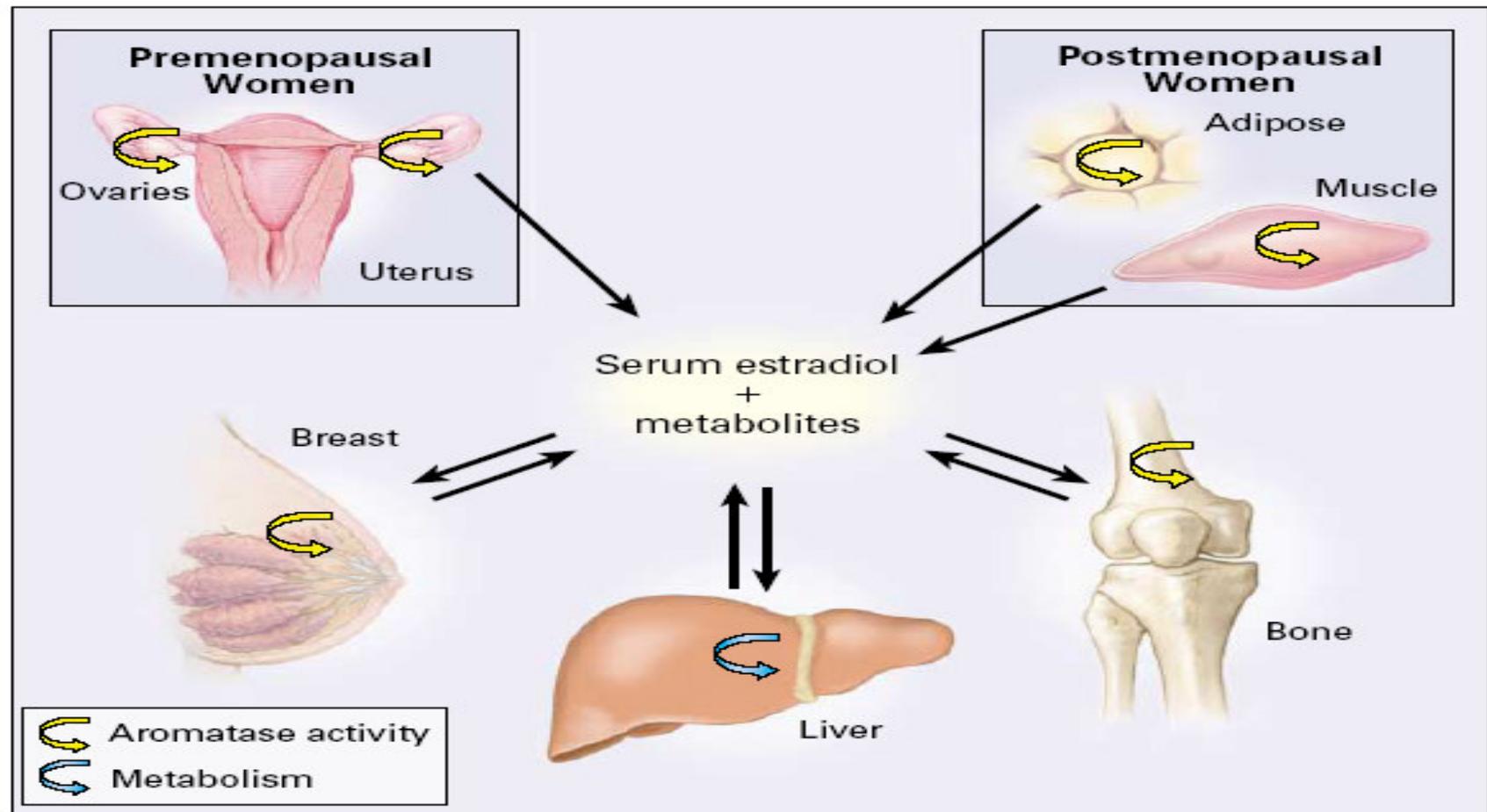
Age <40	74/417 (17.7%)	119/398 (29.9%)	-21.9	44.0		0.61 (SE 0.12)
40-49	173/1119 (15.5%)	219/1139 (19.2%)	-24.8	90.3		0.76 (SE 0.09)
50-59	330/1591 (20.7%)	394/1535 (25.7%)	-45.2	161.7		0.76 (SE 0.07)
60-69	379/1822 (20.8%)	527/1789 (29.5%)	-87.3	200.4		0.65 (SE 0.06)
≥70	62/266 (23.3%)	89/286 (31.1%)	-13.6	29.9		0.63 (SE 0.15)
Age unknown	0/10	0/14				

0<1<2<5=10år

Aromatasehæmmere

- Aromatasehæmmere inde i varmen
 - Anastrozol (Arimidex)
 - Exemestan (Aromasin)
 - Letrozol (Femar)
 - Alle \geq tamoxifen ved tilbagefald
 - Virker kun ved ER-positiv brystkræft
 - Virker kun hos postmenopausale
-

Østrogenproduktion



Østradiol i serum

Præmenopausale	400 pmol/l
Postmenopausale	25 pmol/l
Postmenopausale + aromatasehæmmer	0-5 pmol/l

Adjuvante AI strategier

AI fra start

- BIG1-98
- ATAC
- TEAM
- MA27
- FACE

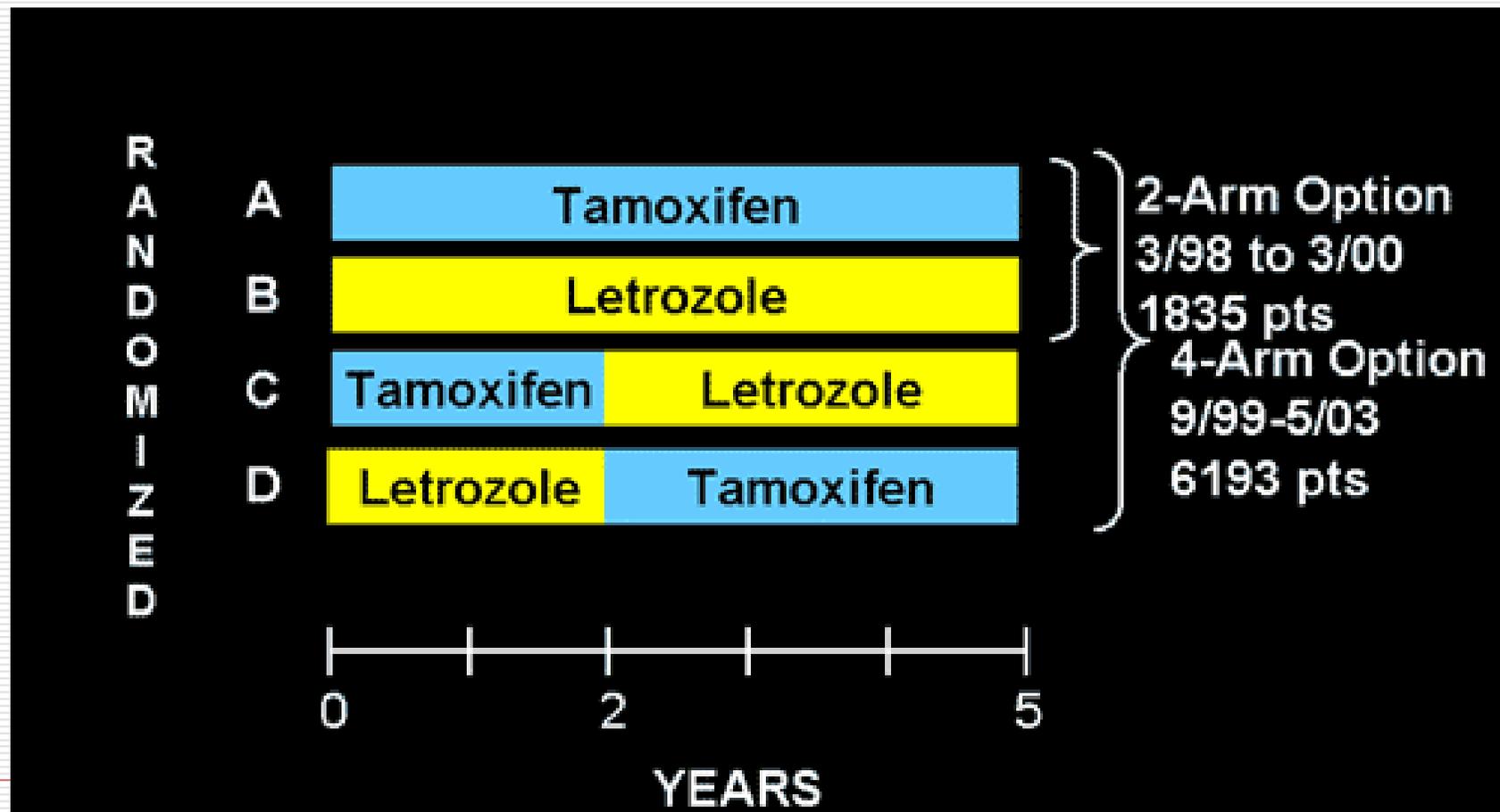
AI extended

- MA17/MA17R
- NASBP B-33
- ABCSG 6a

AI sekventielt

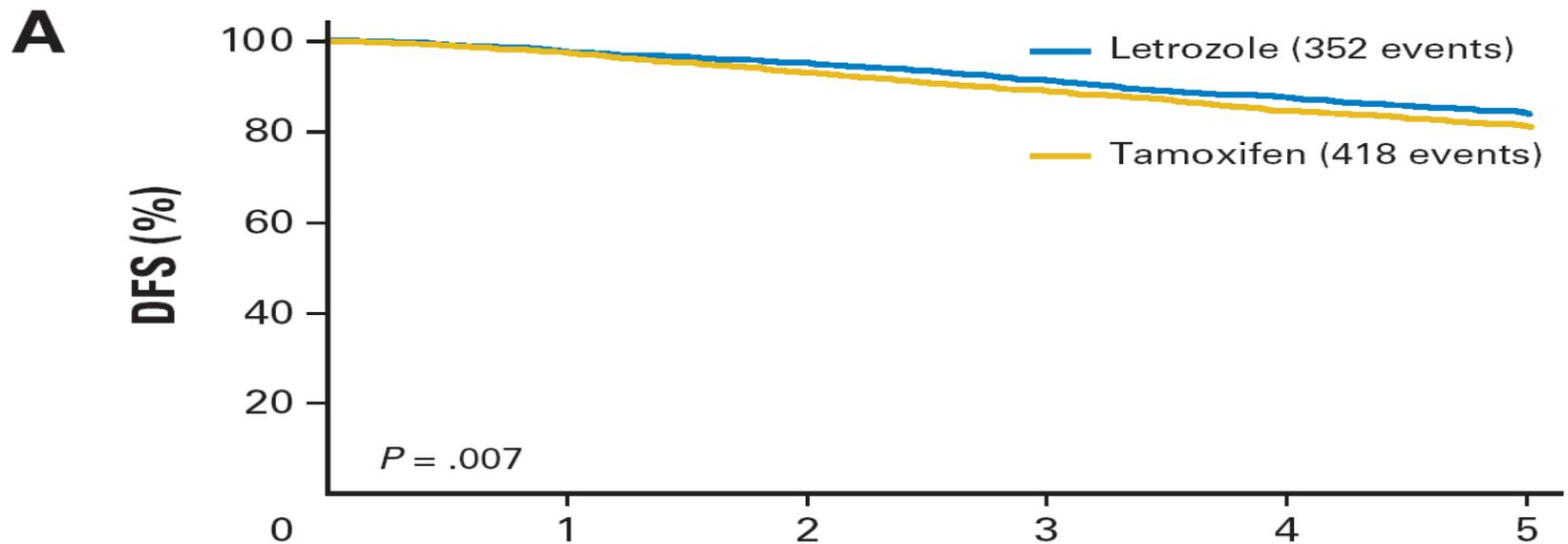
- IES
 - BIG1-98
 - TEAM
 - ARNO
 - ABCSG-8
 - ITA
-

BIG 1-98 – AI fra start



BIG 1-98

Coates, JCO 2007

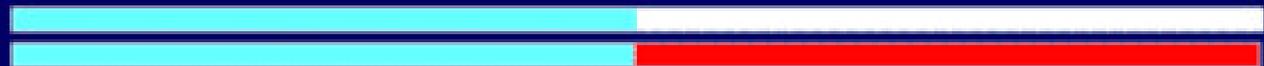


		Years After Random Assignment					
		0	1	2	3	4	5
Letrozole							
No. at risk		2,463	2,393	2,315	1,828	1,215	829
DFS (%)		97.6	95.0	91.2	87.5	84.0	
Tamoxifen							
No. at risk		2,459	2,388	2,266	1,788	1,164	800
DFS (%)		97.4	93.0	88.9	84.6	81.1	

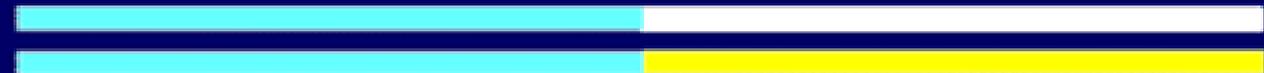
Adjuverende aromatasehæmmere 2

2. Extended Adjuvant (After 5 Years Tamoxifen)

MA-17

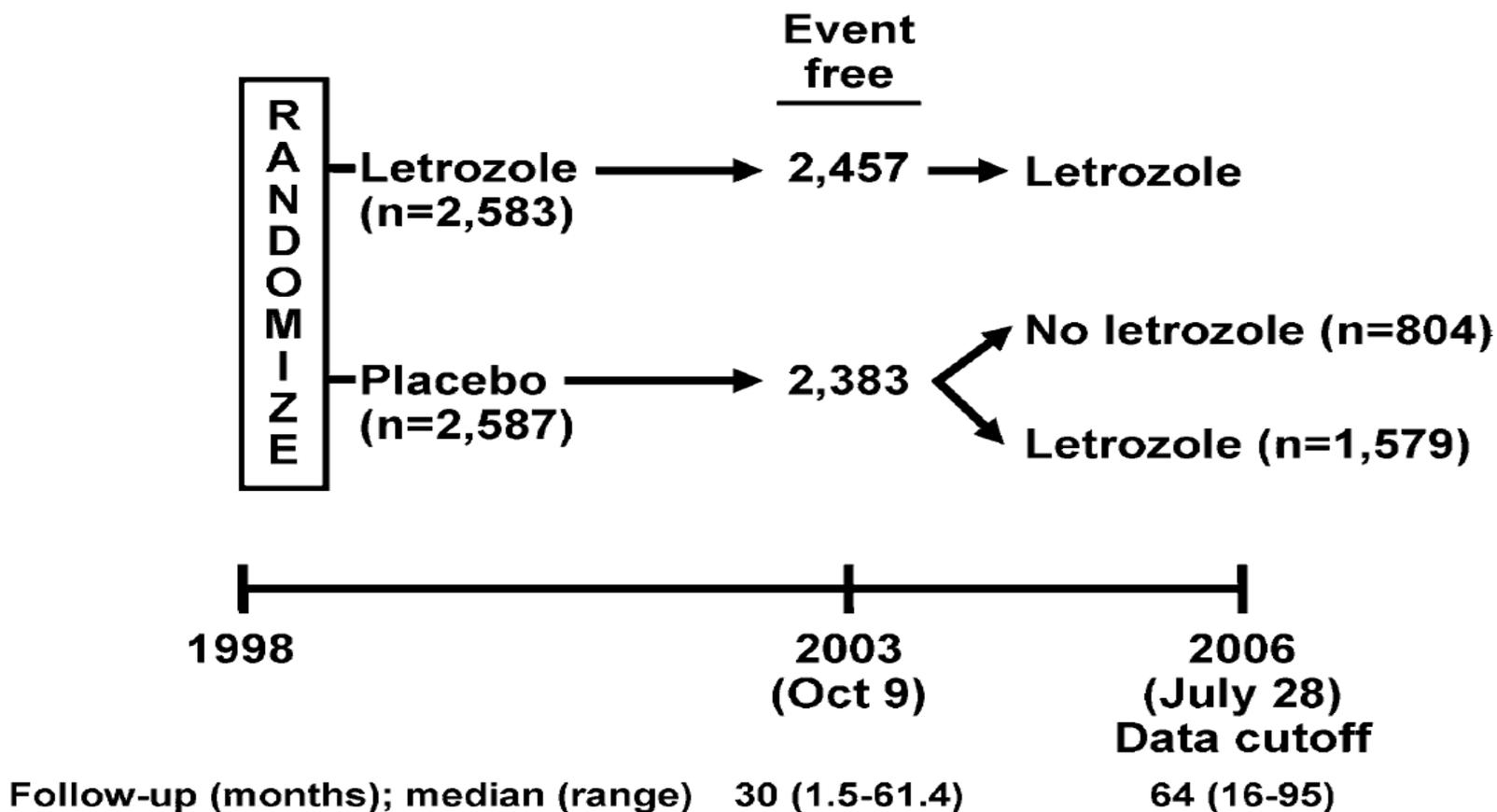


NSABP B33

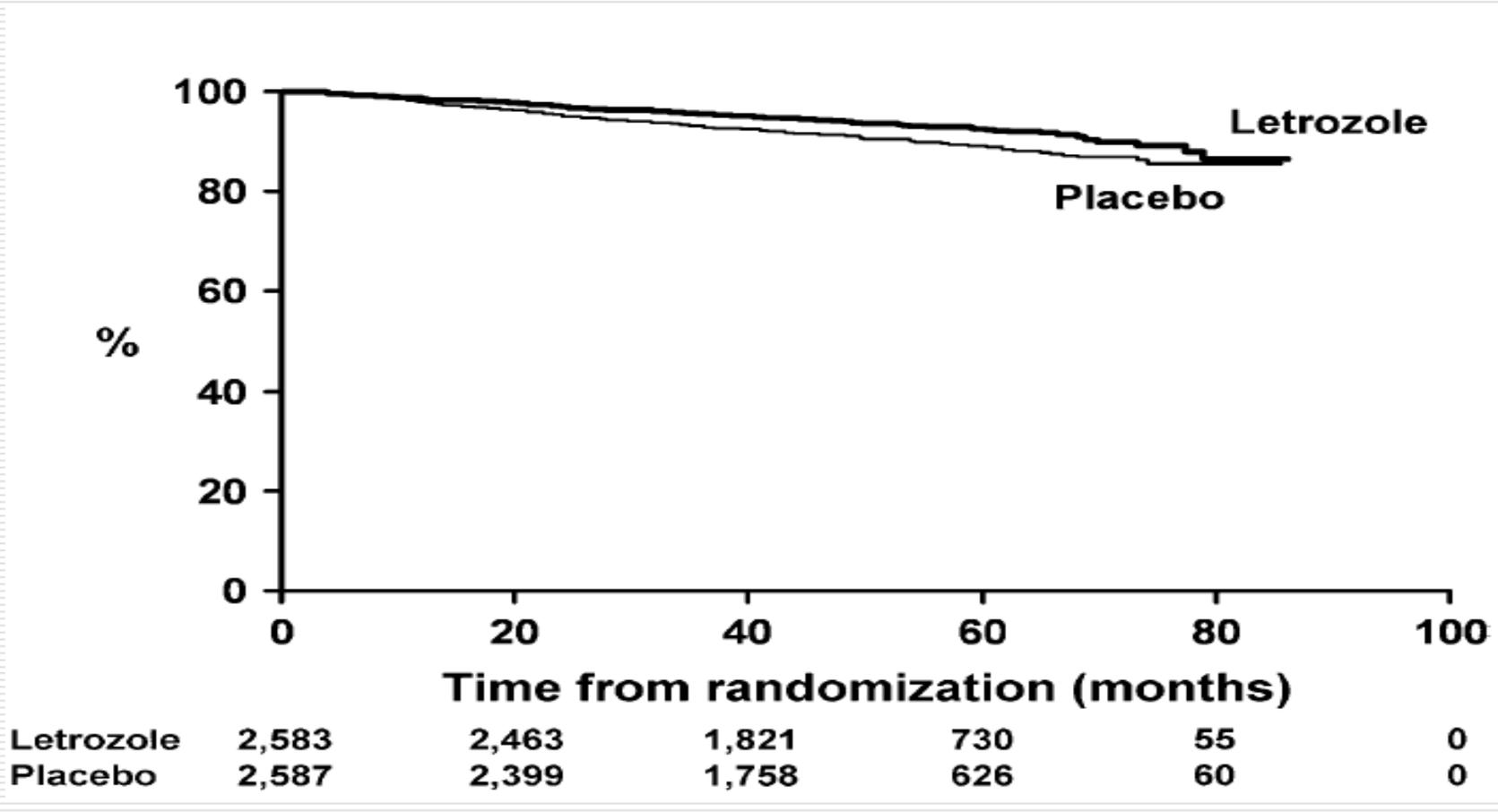


MA-17

Ingle Ann Oncol 2008

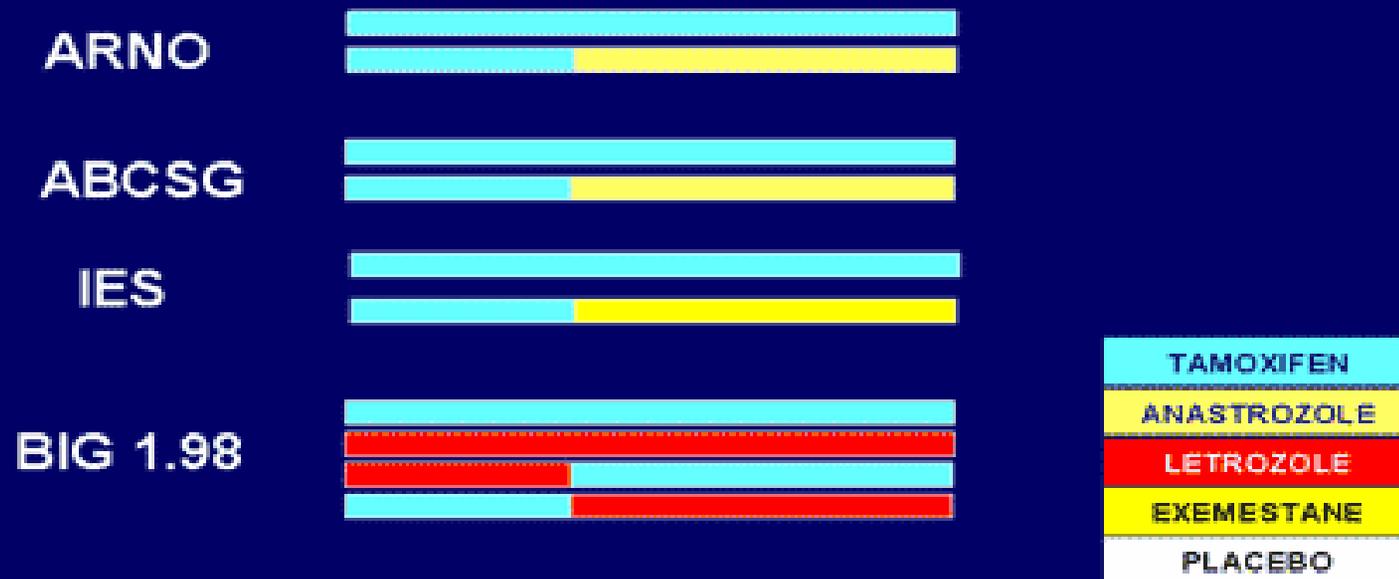


MA 17



Adjuverende aromatasehæmmere 3

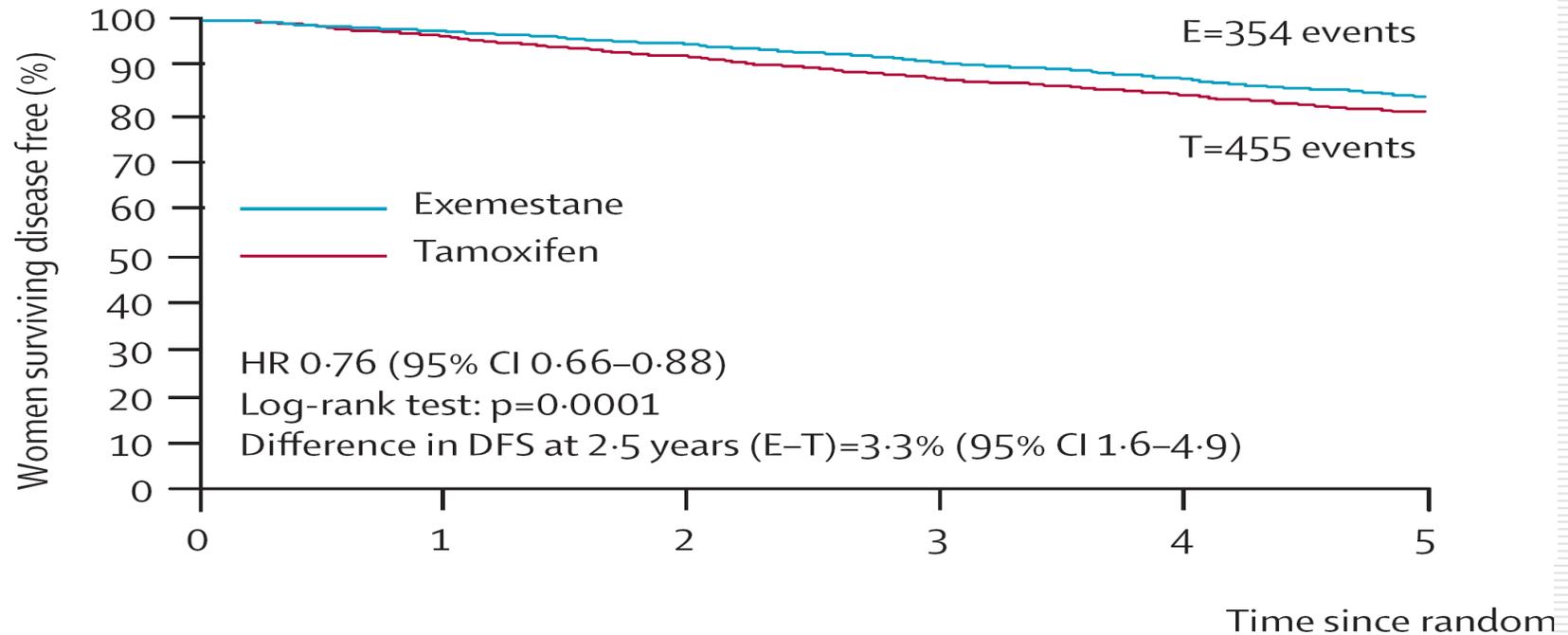
3. Sequential Adjuvant (After 2 Years Tamoxifen)



IES

Coombes, Lancet 2007

ITT



Number of events/at risk

E	0/2352	58/2244	66/2165	83/1954	70/1506
T	0/2372	83/2252	104/2134	103/1898	71/1442

Hvilken strategi?

	Behandling	HR DFS
ATAC	Anastrozol 5 vs Tamoxifen 5	0,87
BIG 1-98	Letrozol 5 vs Tamoxifen 5	0,82
IES	Tamoxifen 2½+exemestan 2½ vs tamoxifen 5	0,76
MA 17	Tamoxifen 5 + Letrozol 5 (2½) vs Tamoxifen 5 + Placebo 5	0,58

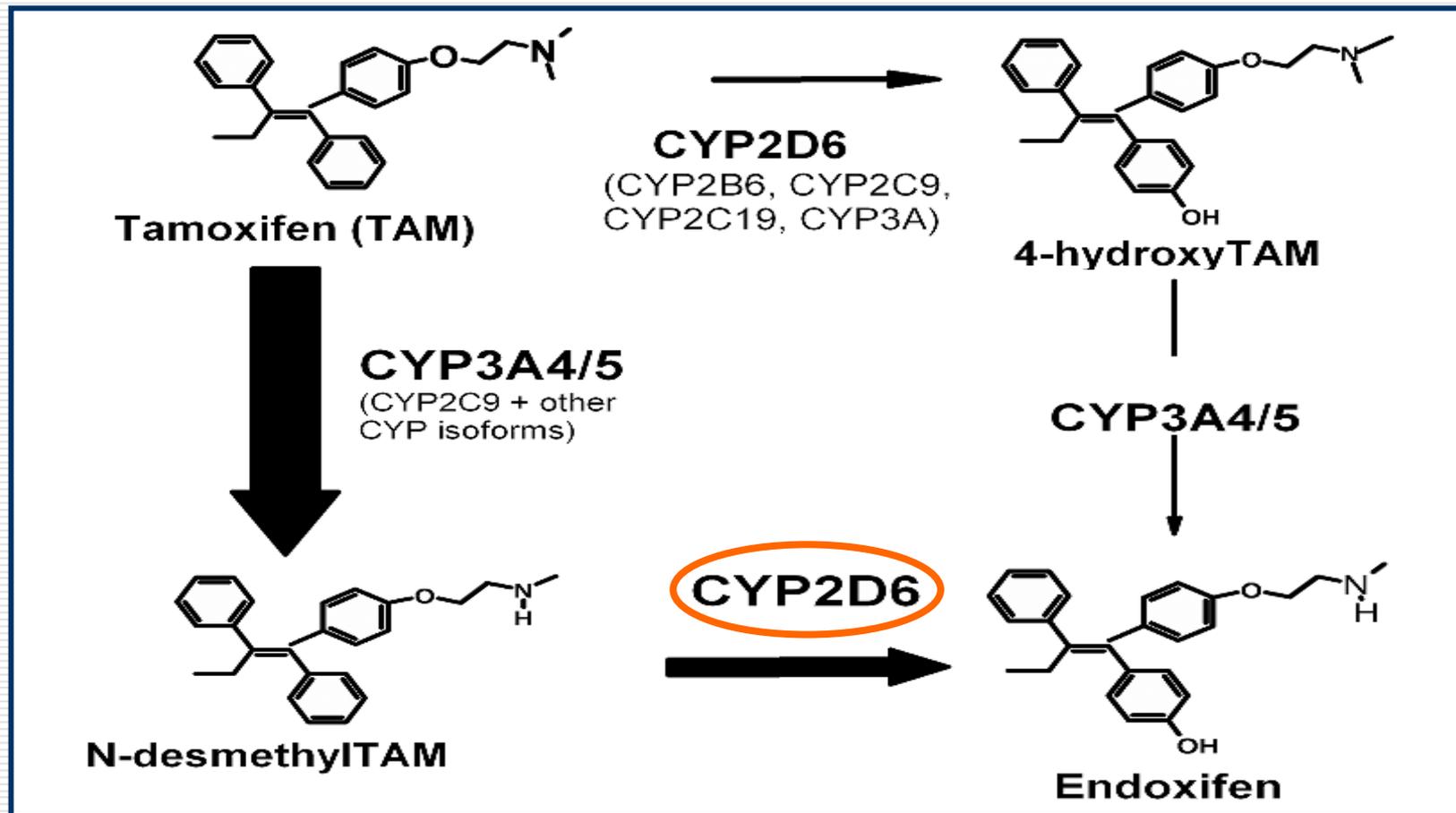
Hvad ved vi så

- AI mere effektive end tamoxifen
 - Tamoxifen mere dvt, pe og gyn tox
 - AI mere skelet- og måske lipidtox
 - Data tyder mest på klasseeffekt
 - Behandlingssekvens og -varighed uafklaret
-

Hvad vil vi gerne vide

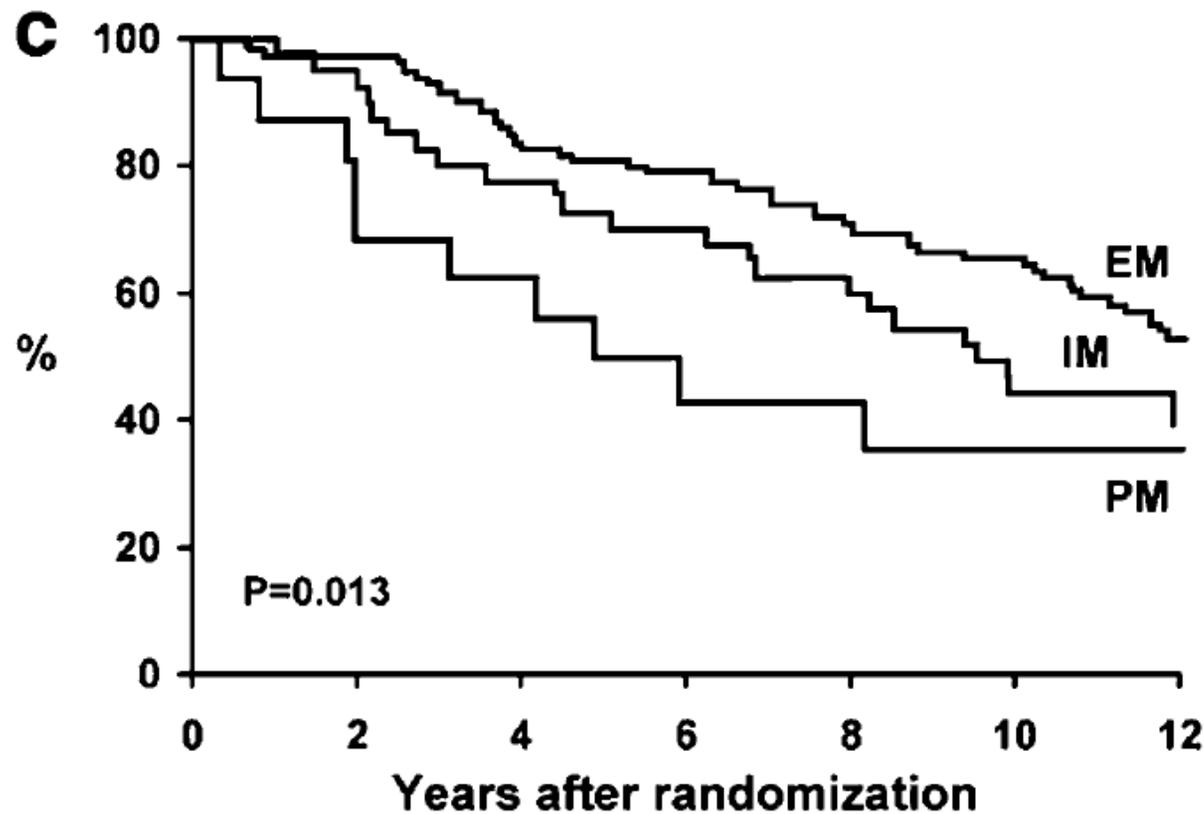
- Er tamoxifen obsolet?
 - AI – hvor længe?
 - AI i kombination?
 - Hvilken AI?
-

Tamoxifen metabolisk pathway



Skindød?

Goetz, Breast Cancer Res Treat 2007



ON THE TREATMENT OF INOPERABLE
CASES OF CARCINOMA OF THE MAMMA:
SUGGESTIONS FOR A NEW METHOD
OF TREATMENT, WITH ILLUSTRATIVE
CASES.¹

BY GEORGE THOMAS BEATSON, M.D. EDIN.,
SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON
GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY
TO THE UNIVERSITY OF EDINBURGH.

Dias nummer 38

- j2** Beatson observerede regression af metastatisk mammacancer hos 3 kvinder efter ooforektomi. Han pyntede lidt på resultaterne for at fremme forståelsen idet man senere fandt at han havde ooforektomeret 7 men kun set respons hos de 3, men det svarer jo fint til dagens responsrater ved 1. liniebehandling

joern; 14-05-2008

j3

"I am satisfied that in the ovary of the female and the testicle of the male we have organs that send out influences more subtle it may be and more mysterious than those emanating from the nervous system, but possibly much more potent than the latter"



Dias nummer 39

j3

Hvad han havde gjort var at fjerne en specifik vækstfaktor, østradiol, fra det cellulære target, østrogenreceptoren.
joern; 14-05-2008