Systemic tratment as a part of multidisciplinary tretment of breast cancer

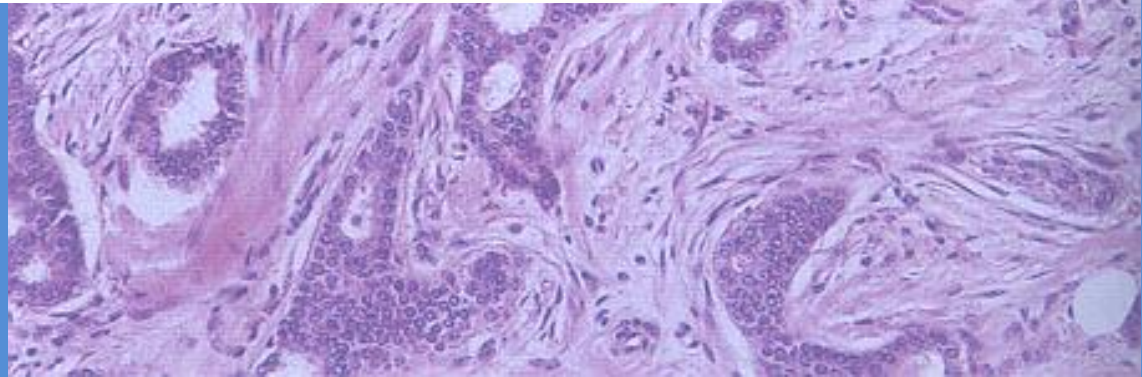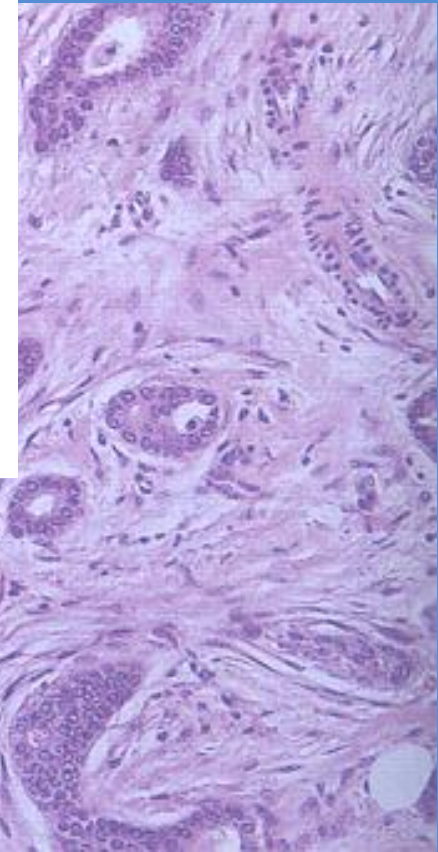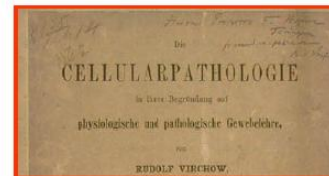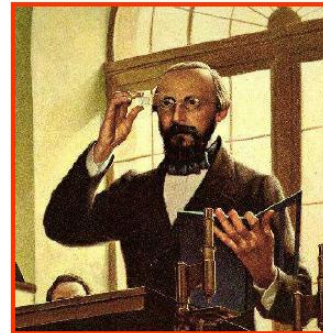Tadeusz Pienkowski

Postgraguate Medical Educational Center

Paris 2013

Prof. Dr. Rudolf Virchow
1821-1902

CELLULARPATHOLOGIE
physiologische und pathologische Gewebelehre,
RUDOLF VIRCHOW.

William Stewart Halsted
W. Halsted 1852-1922

A

B
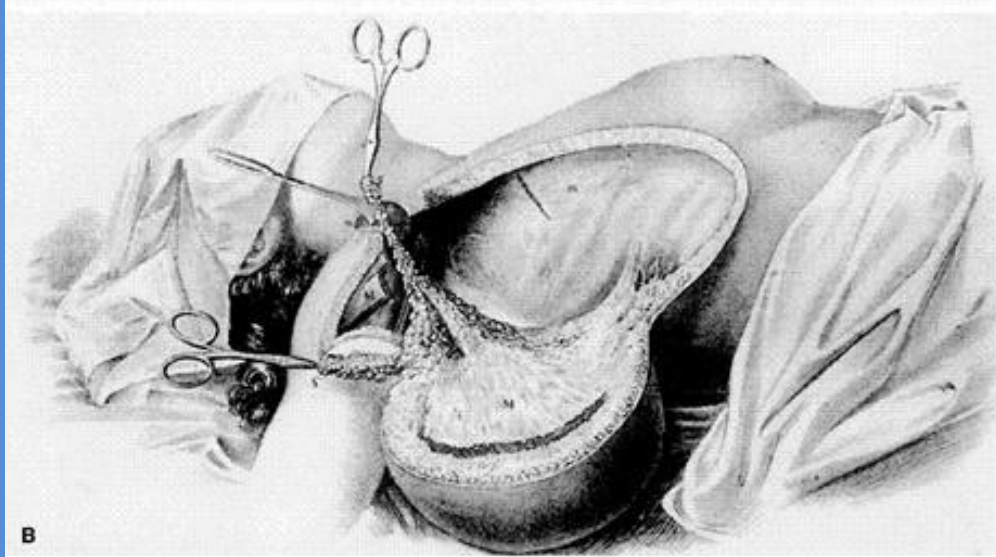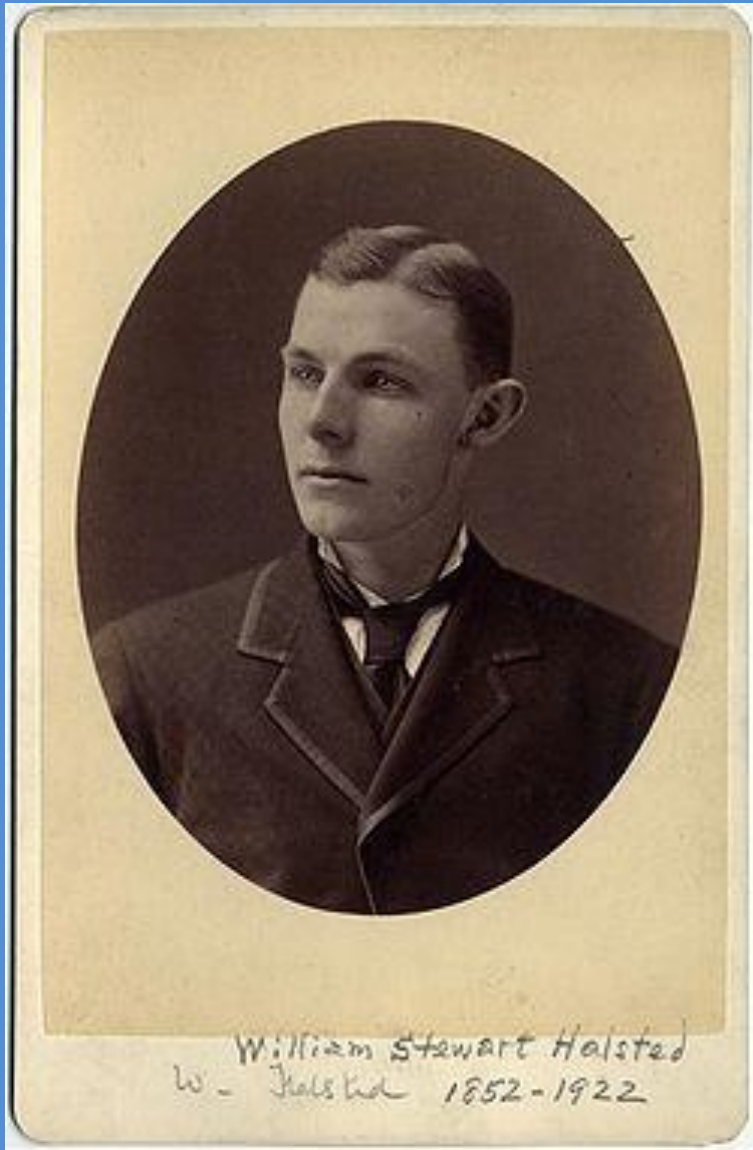
Breast Cancer
Systemic treatment

- Early breast cancer – Adjuvant

Overall survivall

- Localy advanced Neoadjuvant

Overall survivall; Breast conserving treattment

- Disseminated disease

Paliation of symptoms;

- Chemotherapy

- Endocrine treatment

- Target therapies
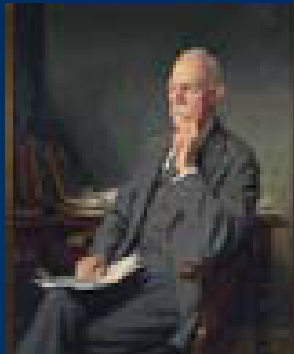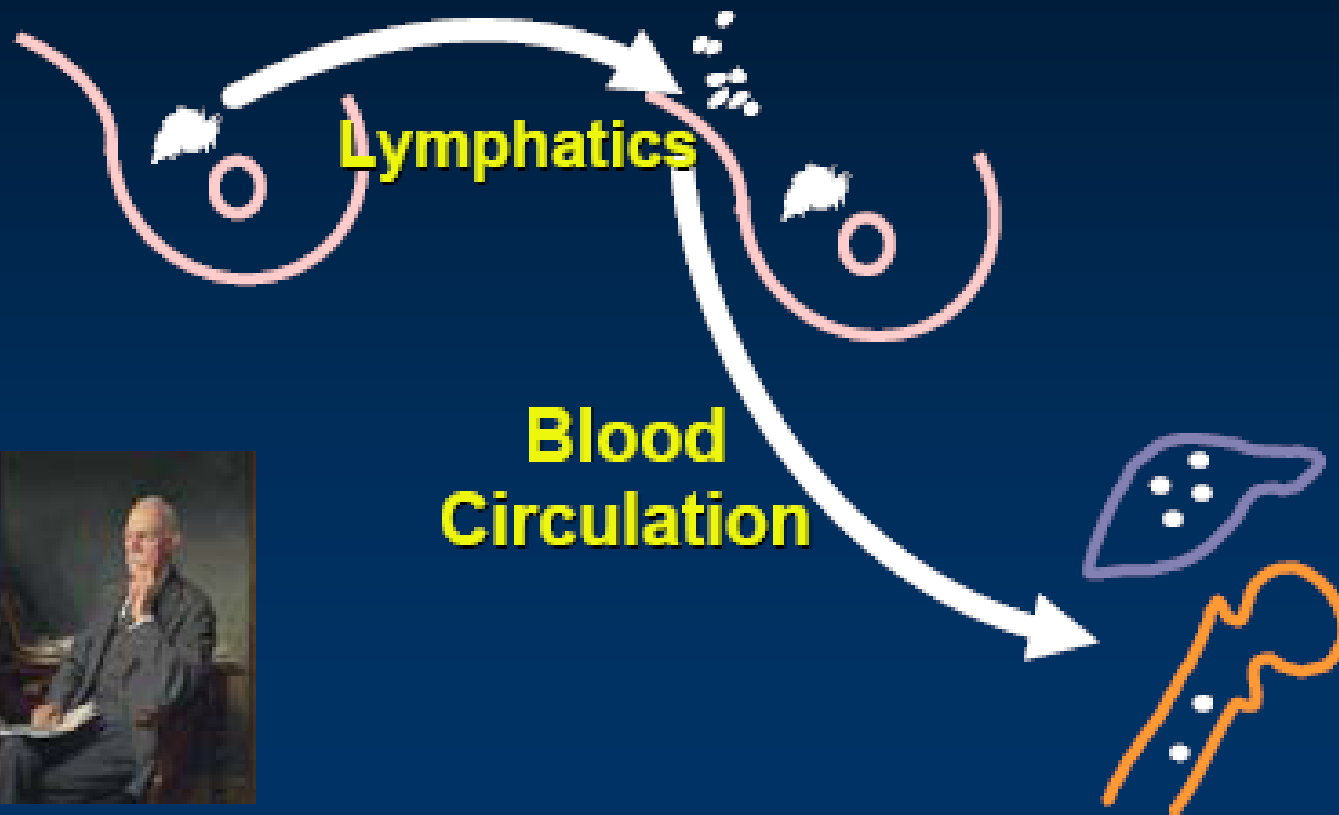
Rak przewodowy inwazyjny
Rokowanie
Guz pierwotny
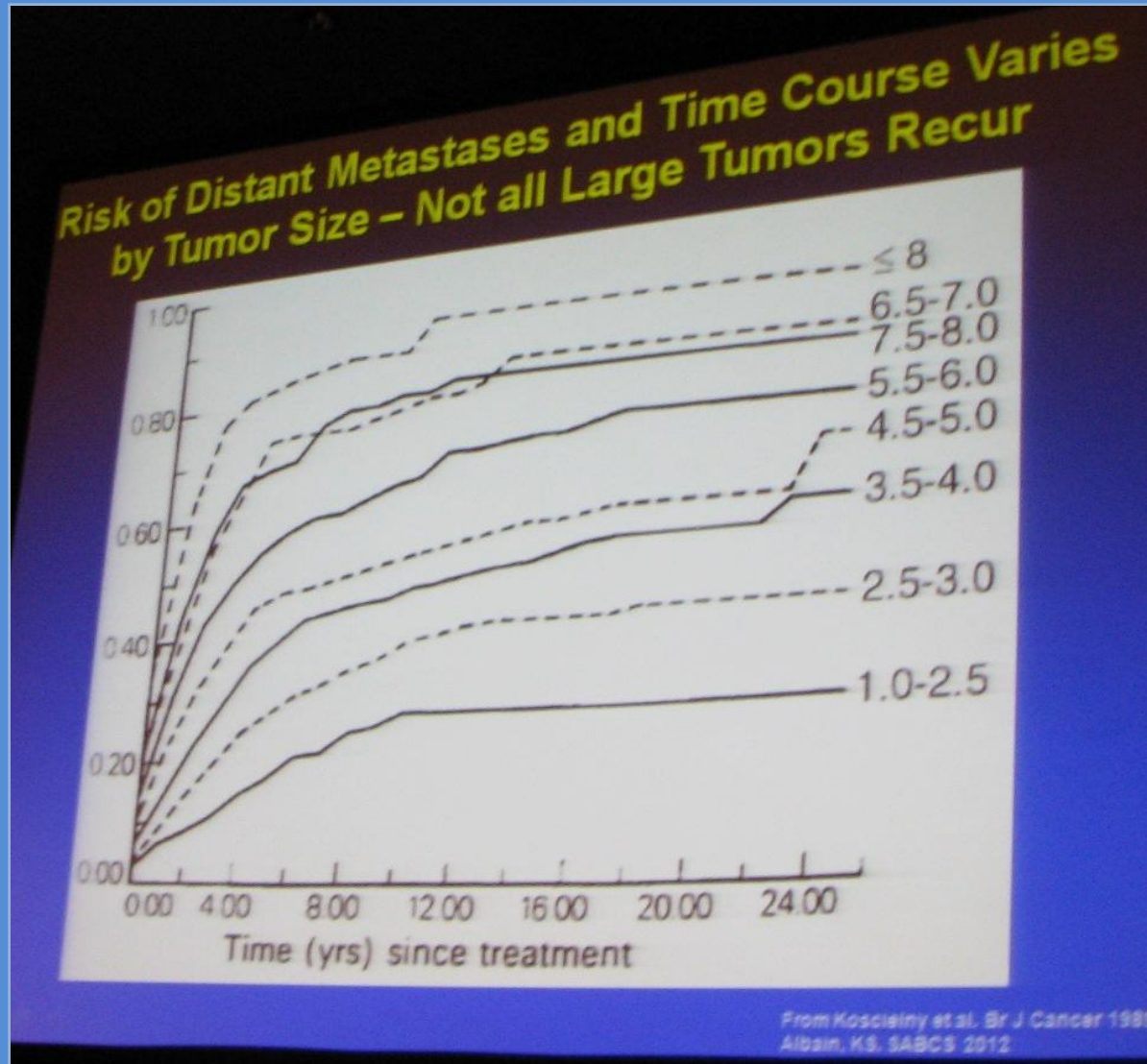
Challenge of Early-Stage Breast Cancer

- Despite surgery, cytotoxic chemotherapy, hormonal therapy, and/or regional radiotherapy, ~ 30% of patients will eventually experience disease recurrence
- The biologic reasons for recurrence and resistance to treatment are poorly understood
- Recurrent breast cancer is usually lethal
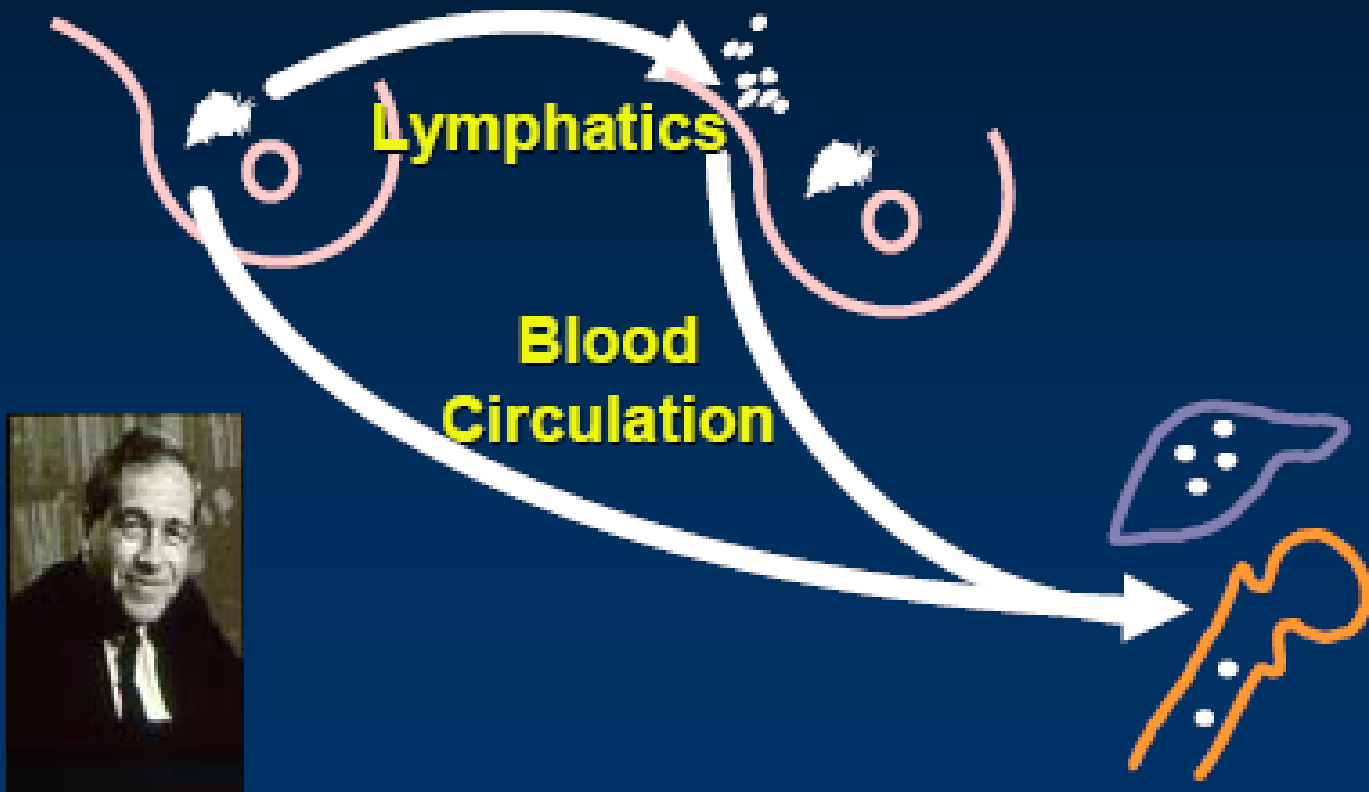
Hallmarks of Malignancy

Growth factor self-sufficiency

Insensitivity to antigrowth signals

Evading apoptosis

Cancer

Sustained angiogenesis

Tissue invasion and metastasis

Limitless replication potential

Hanahan D, et al. Cell. 2000;100:57-70.
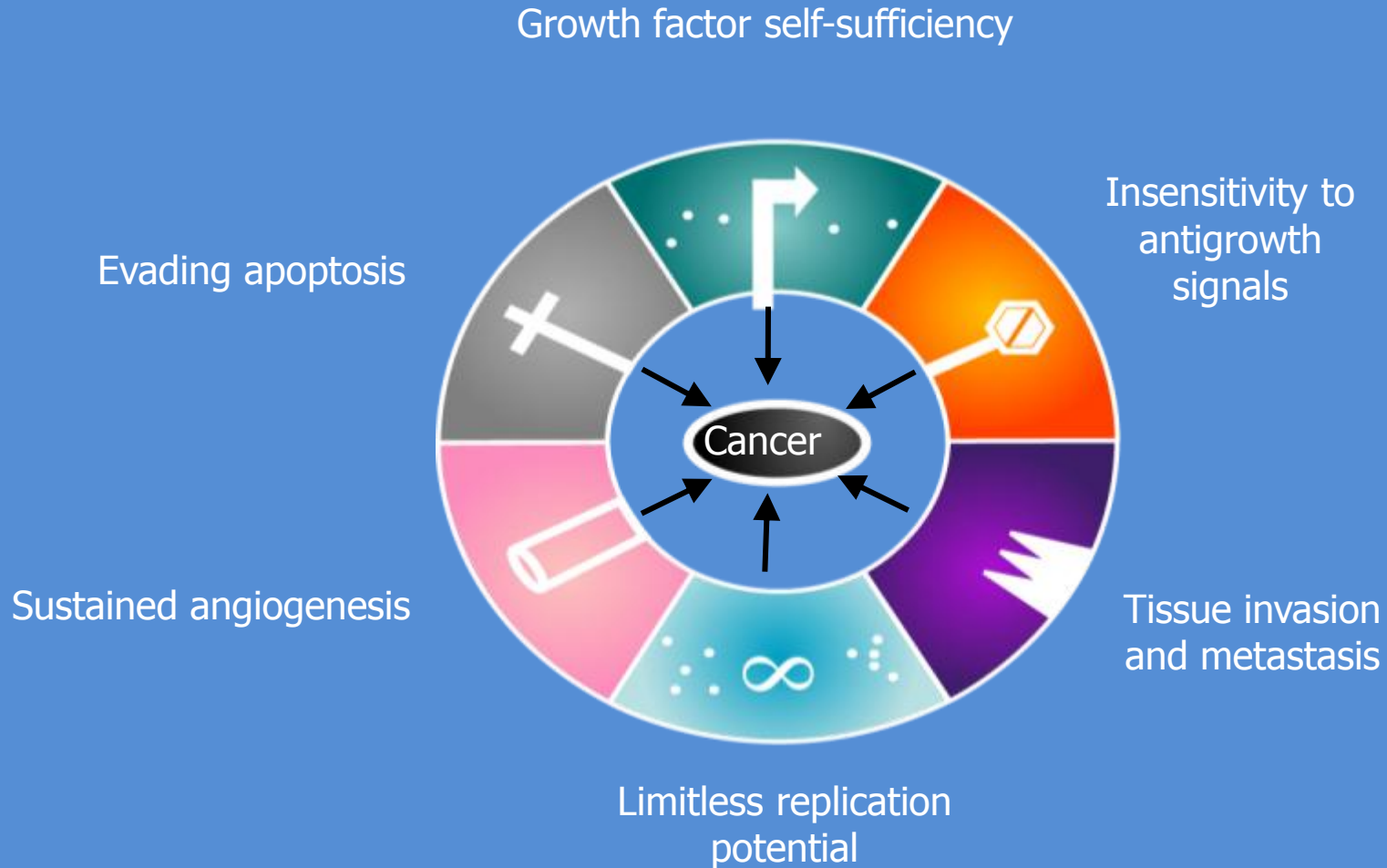
Gene expression array-identified subtypes of Breast Cancer

Unsupervised Hierarchical Clustering of Primary Breast Cancers

Luminal A — ER+ / HER2-
Luminal B — ER+ / HER2+
HER2+/ER- — ER- / HER2+
Basal-like — ER- / HER2- / CK5/6+ and/or HER1+
Normal Breast

ER
HER2
CK 5
HER1
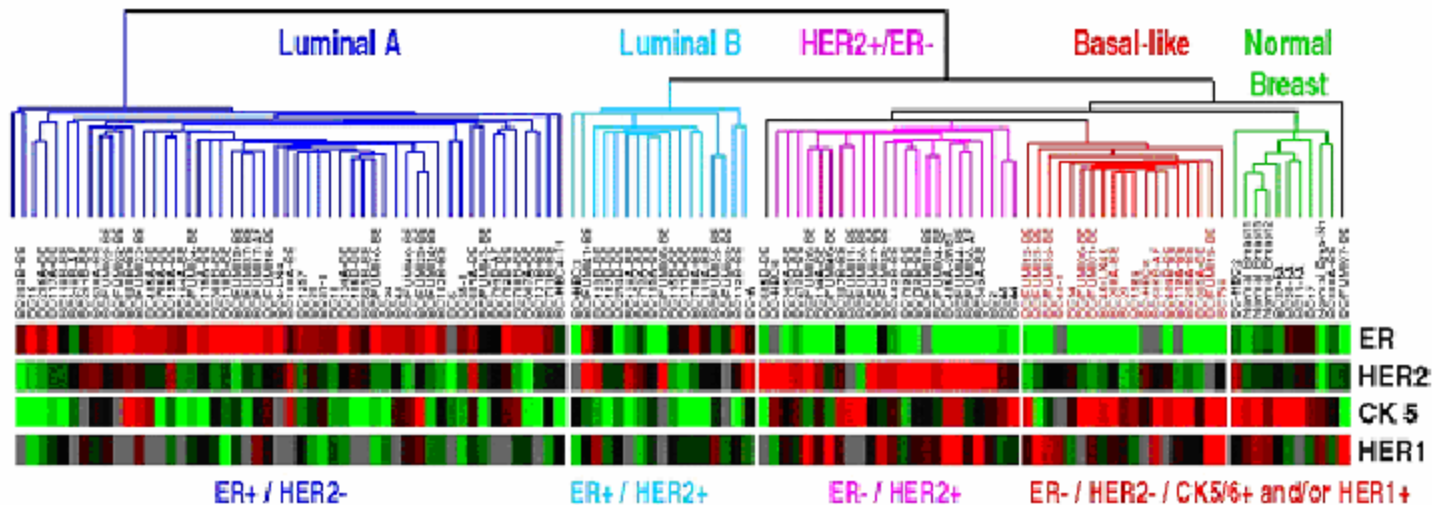
Perou *et al. Nature* 2000;406:747-52.

Breast Cancer
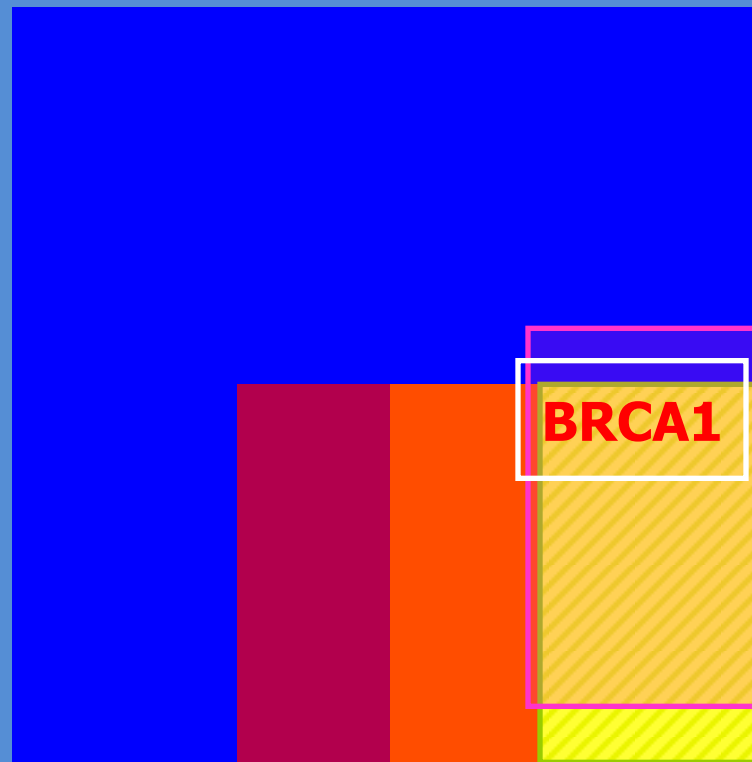
MOLECULAR ORIGINS OF CANCER

Gene-Expression Signatures in Breast Cancer

Christos Sotiriou, M.D., D.Phil., and Lajos Pusztai, M.D., D.Phil.

HER2-Negative

HER2-Positive

ER-Negative

ER-Positive

ER-Positive or ER-Negative

Good Differentiation Low Ki-67

Poor Differentiation High Ki-67

Pathological Variables	Basal-like (%)	Luminal A (%)	Luminal B (%)	HER2-like (%)
HER2-positive (IHC)	10	12	20	100
ER-positive (IHC)	12	96	97	46
Grade III	84	19	53	74
Tumor size >2 cm	75	53	69	74
Node-positive	40	52	65	66

Figure 1. Correspondence between Molecular Class and Clinicopathological Features of Breast Cancer.

Data are from Sorlie et al.,[3] Hu et al.,[5] Rouzier et al.,[28] and van de Vijver et al.[29] HER2 status, as determined by immunohistochemical (IHC) analysis, was available for only 82 of 535 patients in the combined studies. ER denotes estrogen receptor, and Ki-67 nuclear antigen Ki-67.

Breast Cancer Relapse is Heterogeneous
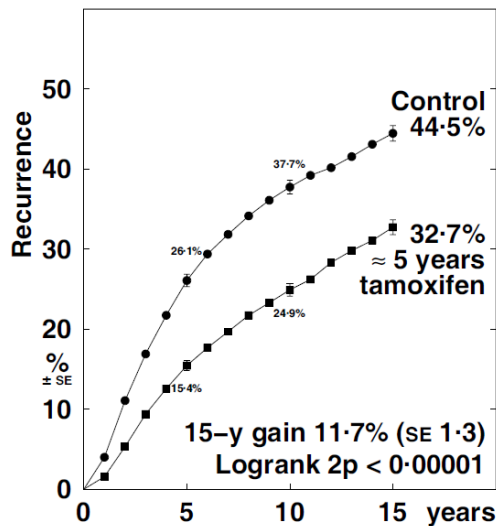
Anderson et al, Breast Cancer Res Treat 2006

≈ 5 years tamoxifen vs. Not — RECURRENCE — ER+ PR+

Recurrence (% ± SE)

Control 44·5%

32·7% ≈ 5 years tamoxifen

37·7%
26·1%
24·9%
15·4%

15–y gain 11·7% (SE 1·3)
Logrank 2p < 0·00001

Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	3·43 (562 / 16381)	2·48 (298 / 11999)	2·21 (160 / 7226)	1·92 (58 / 3015)
Control	6·00 (906 / 15108)	3·51 (353 / 10069)	2·22 (133 / 5984)	2·15 (52 / 2416)
Rate ratio, from	0·55 SE 0·04	0·68 SE 0·07	0·98 SE 0·12	0·85 SE 0·18
(O−E) / V	−204·2 / 342·6	−59·0 / 154·2	−1·7 / 69·6	−4·3 / 25·7

≈ 5 years tamoxifen vs. Not — RECURRENCE — ER+ PR–poor
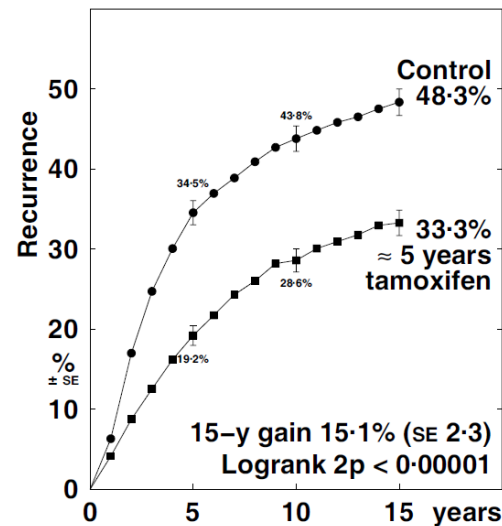
Recurrence (% ± SE)

Control 48·3%

33·3% ≈ 5 years tamoxifen

43·8%
34·5%
28·6%
19·2%

15–y gain 15·1% (SE 2·3)
Logrank 2p < 0·00001

Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	4·42 (215 / 4865)	2·60 (92 / 3536)	1·44 (35 / 2430)	1·53 (20 / 1308)
Control	8·55 (378 / 4420)	3·08 (89 / 2889)	1·71 (33 / 1934)	1·20 (13 / 1080)
Rate ratio, from	0·50 SE 0·06	0·82 SE 0·14	0·83 SE 0·23	1·16 SE 0·40
(O−E) / V	−91·7 / 133·7	−8·1 / 41·7	−3·1 / 16·0	1·0 / 7·1

≈ 5 years tamoxifen vs. Not — RECURRENCE — ER–poor PR+

Recurrence (% ± SE)

Control 32·4%
31·0% ≈ 5 years tamoxifen

32·4%
25·9%
31·0%
20·8%

10–y gain 1·4% (SE 2·9)
Logrank 2p = 0·37
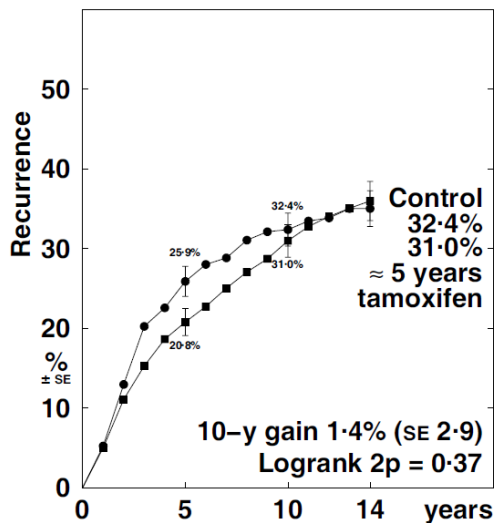
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Tamoxifen	4·65 (121 / 2600)	2·77 (46 / 1663)	1·88 (12 / 638)
Control	6·22 (156 / 2510)	1·89 (30 / 1586)	1·06 (7 / 663)
Rate ratio, from	0·78 SE 0·11	1·31 SE 0·29	2·01 SE 0·69
(O−E) / V	−15·5 / 60·8	4·4 / 16·0	3·1 / 4·4

≈ 5 years tamoxifen vs. Not — RECURRENCE — ER–poor PR–poor
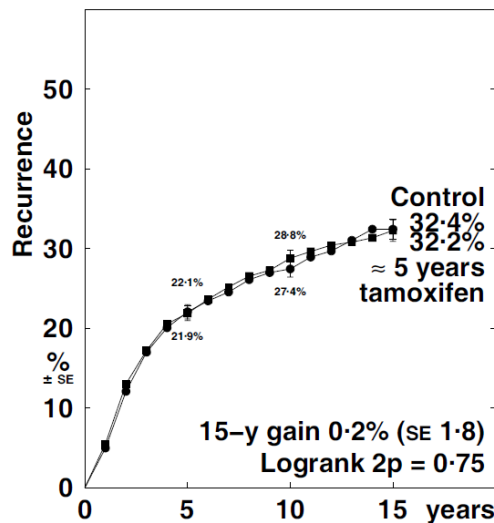
Recurrence (% ± SE)

Control 32·4%
32·2% ≈ 5 years tamoxifen

28·8%
22·1%
27·4%
21·9%

15–y gain 0·2% (SE 1·8)
Logrank 2p = 0·75

Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	5·18 (499 / 9631)	1·87 (111 / 5944)	1·04 (23 / 2214)	1·60 (6 / 375)
Control	5·06 (481 / 9506)	1·51 (91 / 6024)	1·58 (38 / 2410)	0·81 (4 / 495)
Rate ratio, from	1·00 SE 0·07	1·27 SE 0·16	0·63 SE 0·21	1·46 SE 0·79
(O−E) / V	−0·6 / 222·0	11·6 / 48·7	−6·6 / 14·3	0·9 / 2·4

2010 EBCTCG

RECURRENCE in trials of tamoxifen for about 5 years versus the same management, but no tamoxifen

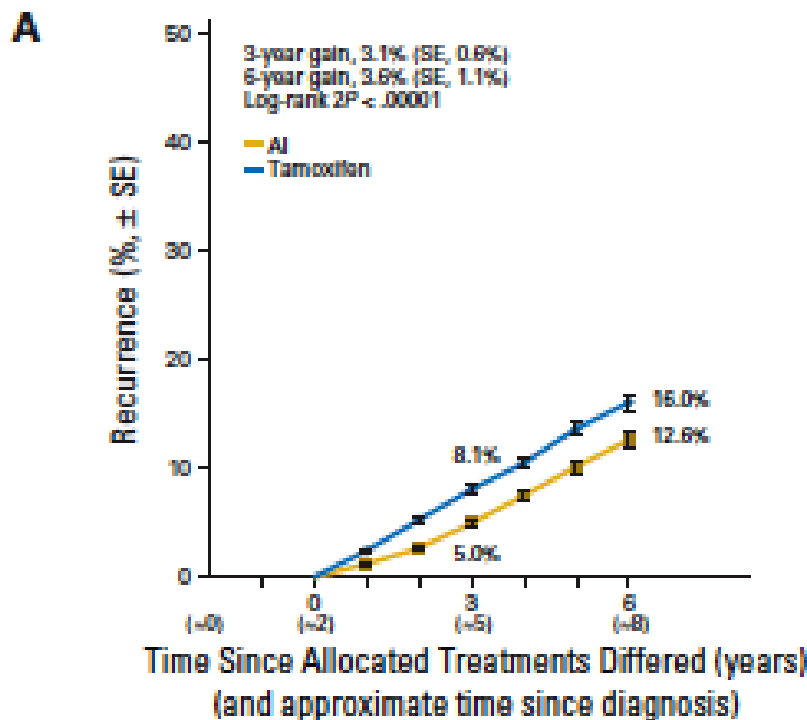| Category	Events/woman–years Allocated tamoxifen	Allocated control	Tamoxifen events Logrank O−E	Variance of O−E	Ratio of annual event rates Tamoxifen : Control
ER = 0	159/4970 (3·2%/y)	158/5776 (2·7%/y)	7·1	68·3	1·11 (SE 0·13)
ER 1 − 3	197/6516 (3·0%/y)	186/6194 (3·0%/y)	1·4	83·9	1·02 (SE 0·11)
ER 4 − 9	178/5374 (3·3%/y)	183/5498 (3·3%/y)	−6·3	75·9	0·92 (SE 0·11)
Other ER–poor	436/9273 (4·7%/y)	440/8757 (5·0%/y)	−16·0	191·4	0·92 (SE 0·07)
ER unknown	495/20089 (2·5%/y)	612/16486 (3·7%/y)	−85·8	244·0	0·70 (SE 0·05)
ER 10 − 19	230/8034 (2·9%/y)	312/7192 (4·3%/y)	−45·6	119·9	0·68 (SE 0·08)
ER 20 − 29	157/5032 (3·1%/y)	194/4596 (4·2%/y)	−26·8	76·2	0·70 (SE 0·10)
ER 30 − 49	231/7999 (2·9%/y)	258/6817 (3·8%/y)	−29·6	110·9	0·77 (SE 0·08)
ER 50 − 99	291/10528 (2·8%/y)	355/8770 (4·0%/y)	−69·4	144·3	0·62 (SE 0·07)
ER 100 − 199	206/8187 (2·5%/y)	337/7205 (4·7%/y)	−78·9	120·4	0·52 (SE 0·07)
ER 200+	208/7938 (2·6%/y)	311/6326 (4·9%/y)	−76·8	114·6	0·51 (SE 0·07)
Other ER+	289/7394 (3·9%/y)	383/6565 (5·8%/y)	−64·8	150·4	0·65 (SE 0·07)
Total	3077/ 101334 (3·0%/y)	3729/ 90182 (4·1%/y)	−491·5	1500·0	0·721 (SE 0·022) 2p < 0·00001

■ 99% or ◁▷ 95% confidence intervals

0   0·5   1·0   1·5   2·0

Tamoxifen better | Tamoxifen worse

Heterogeneity between 9 categories: $\chi^2_8 = 57\cdot0$; p < 0·00001

Treatment effect 2p < 0·00001

Meta analisys;
5 years AI vs tamoxifen

A

5-year gain, 2.9% (SE, 0.7%)
9-year gain, 3.9% (SE, 1.0%)
Log-rank 2P < .00001

— AI
— Tamoxifen

Recurrence (%, ± SE)

12.6%

19.2%
15.3%

9.6%

Time (years)

Recurrence rates (% / year) and log-rank analyses

	Years 0–1	Years 2–4	Years 5+
AI	1.69 (163 / 9,647)	2.31 (261 / 11,297)	2.33 (160 / 6,879)
Tamoxifen	2.46 (234 / 9,510)	2.81 (307 / 10,938)	2.78 (180 / 6,478)
Rate ratio, from	0.67 (SE, 0.08)	0.81 (SE, 0.08)	0.83 (SE, 0.10)
(O–E) / V	-38.4 / 96.6	-29.5 / 137.9	-15.7 / 83.0

B

5-year gain, 1.1% (SE, 0.5%)
9-year gain, 0.5% (SE, 0.8%)
Log-rank 2P = .1

— AI
— Tamoxifen

Breast Cancer Mortality (%, ± SE)

5.9%

10.5%
10.0%

4.8%

Time (years)

Death rates (%/year: total rate—rate in women without recurrence) & log-rank analyses

	Years 0–1	Years 2–4	Years 5+
AI	0.59 (SE, 0.08)	1.26 (SE, 0.10)	1.78 (SE, 0.16)
Tamoxifen	0.57 (SE, 0.08)	1.60 (SE, 0.12)	1.79 (SE, 0.16)
Rate ratio, from	1.01 (SE, 0.19)	0.77 (SE, 0.10)	1.01 (SE, 0.13)
(O–E) / V	0.2 / 27.5	-20.5 / 80.2	0.4 / 61.5

Meta analysis
2-3 years AI vs TAM after   2-3 years tamoxifen
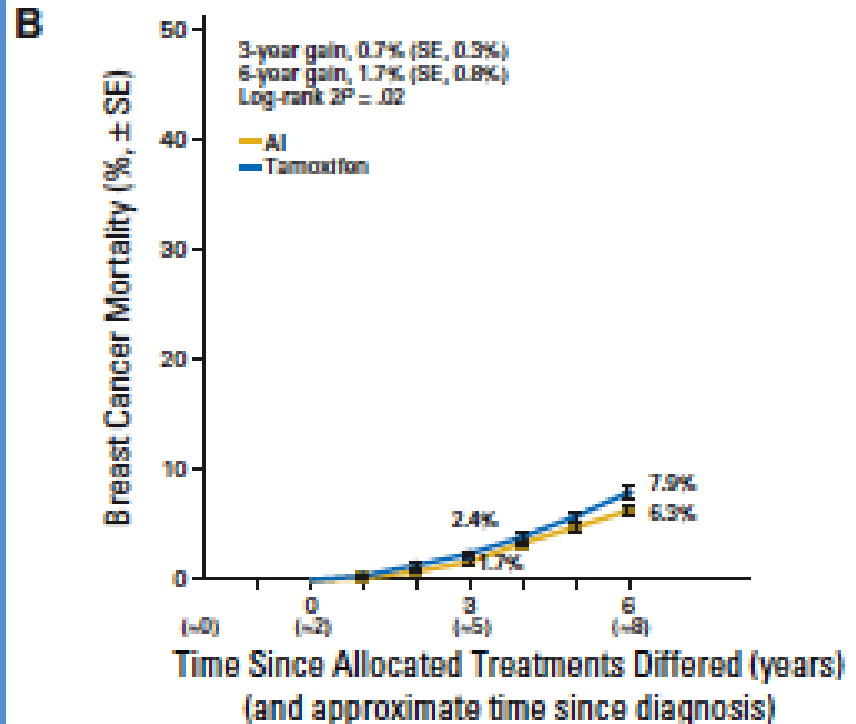
HER-2/neu Positivity Correlates with Decreased Survival in Breast Cancer
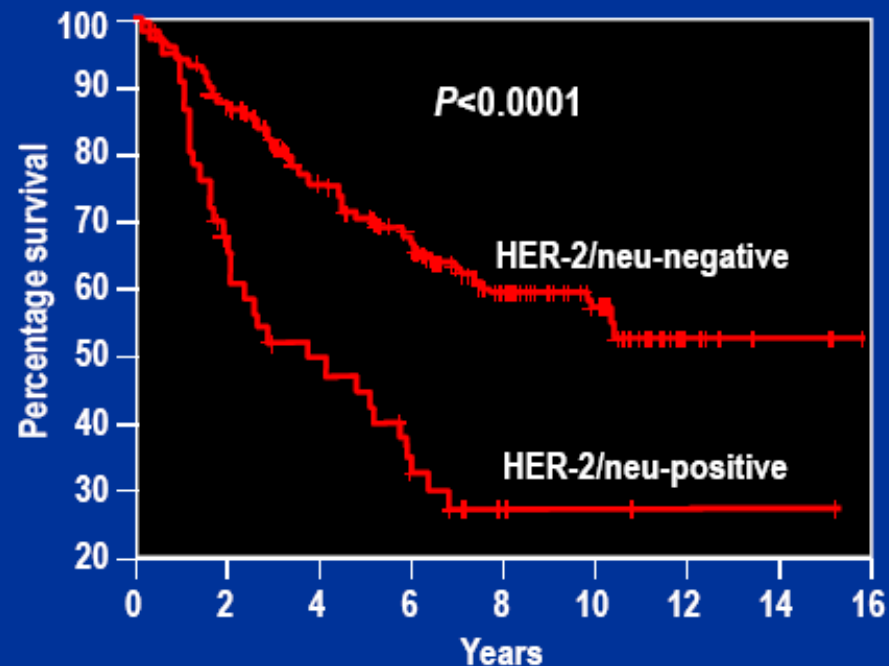
Wiliam CJ et al. J. Pathol. 2003
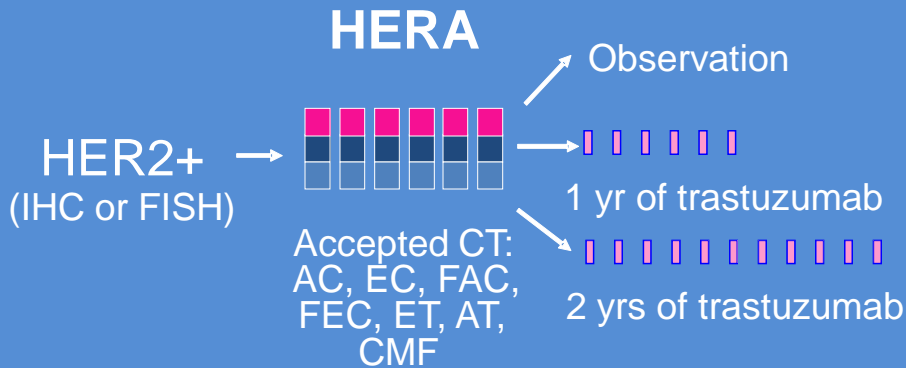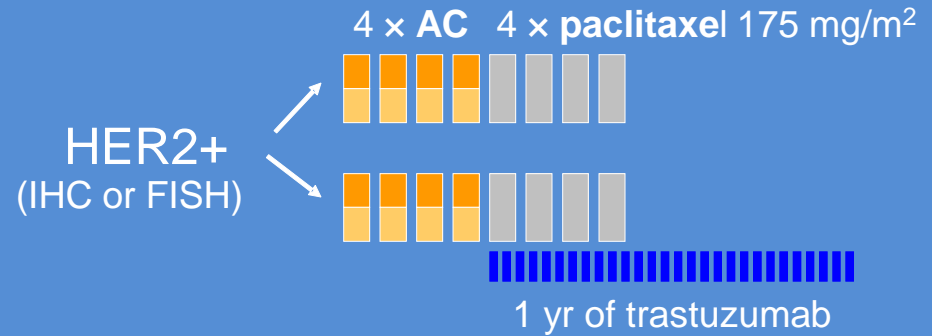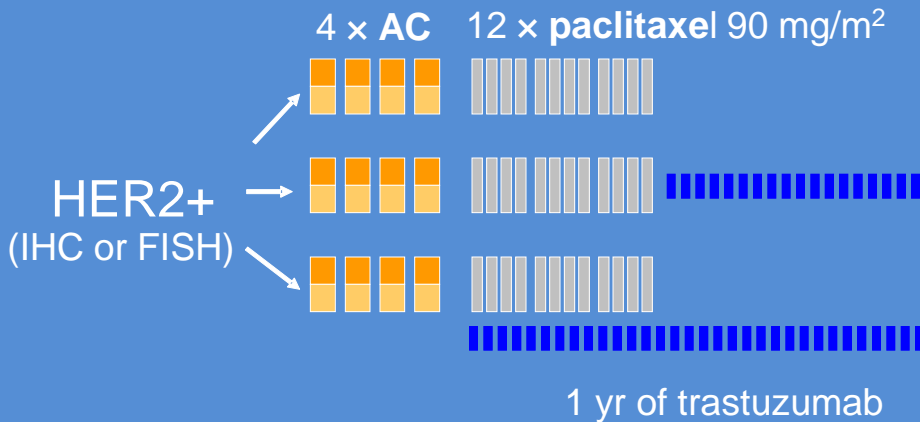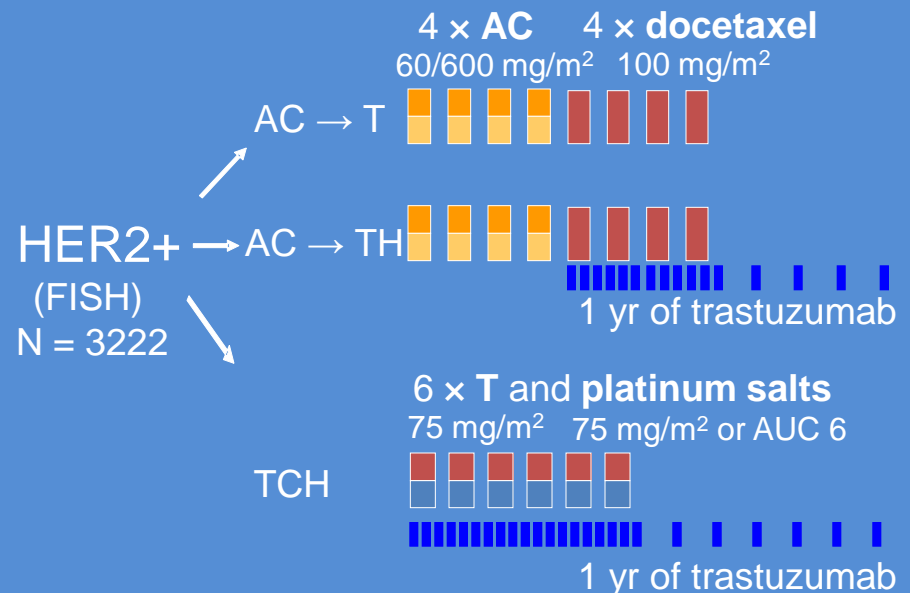
Trastuzumab: adjuvant treatment

Trial	Median follow up	OS HR (95% CI)
HERA Sequential H 65% crossed over to H	8 years	75,5% HR 0,76 P=0.0005
NSABP B-31 NCCTG N9831 Joint analisys	4 years	91% HR 0,67 (0,48- 0, 93) p = 0,015
FINHER 9 weeks H	3 years	95% HR 0,41(0,16-1,08)
BCIRG 006 No ADM arm	5 years	92% HR 0,63 (0,48-0,81) p <0,001 91% HR 0,77(0,60-0,99) p = 0,038
PACS-04 Sequential H	4 years	95% HR 1.27 (0.68-2.38)

Incidence of CHF in Adjuvant Breast Cancer Studies

Study, %	Trastuzumab	Control
B-31/NCCTG	2	0.4
HERA	2	0.3
BCIRG 006		
▪ AC → TH	2	0.4
▪ TCH	**0.4**	0.4

Recurrence

Control
47·4%

34·6%

39·6%
Anthr.

26·2%

% ± SE

10-y gain 7·8% (SE 1·2)
Logrank 2p < 0·00001

0   5   10 years
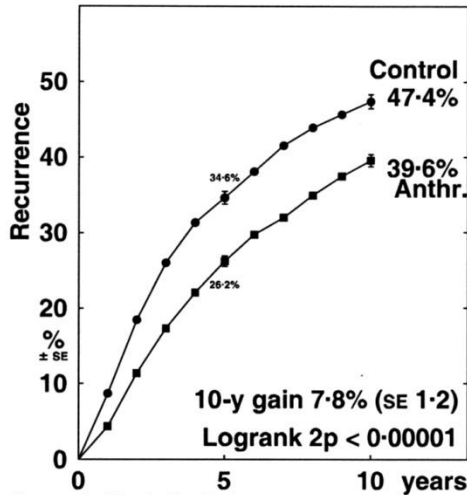
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	6·17 (1184 / 19190)	4·08 (489 / 11981)	2·91 (161 / 5530)
Control	9·06 (1259 / 13899)	4·56 (365 / 8011)	3·90 (160 / 4104)
Rate ratio, from	0·69 se 0·04	0·90 se 0·07	0·73 se 0·11
(O–E) / V	−185·2 / 493·3	−18·3 / 175·9	−20·9 / 66·2

13:08:34 15 June 2010
Not for publication or citation

Breast cancer mortality

Control
35·7%

21·0%

29·3%
Anthr.

15·9%

% ± SE

10-y gain 6·4% (SE 1·2)
Logrank 2p < 0·00001

0   5   10 years

Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	3·38 se 0·13	3·57 se 0·16	2·83 se 0·19
Control	4·77 se 0·17	4·31 se 0·21	2·98 se 0·22
Rate ratio, from	0·73 se 0·05	0·83 se 0·07	0·93 se 0·11
(O–E) / V	−97·8 / 308·5	−35·0 / 193·8	−5·8 / 81·6

13:05:59 15 June 2010
Not for publication or citation

Any death

Control
39·6%

23·1%

34·7%
Anth.

18·0%

% ± SE

10-y gain 4·9% (SE 1·2)
Logrank 2p < 0·00001

0   5   10 years

Death rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	3·91 (811 / 20718)	4·62 (645 / 13969)	4·39 (337 / 7680)
Control	4·93 (834 / 15889)	4·93 (492 / 9975)	4·34 (259 / 5969)
Rate ratio, from	0·75 se 0·05	0·93 se 0·06	0·99 se 0·09
(O–E) / V	−100·2 / 348·4	−18·4 / 236·1	−1·0 / 121·2

15:16:39 21 June 2010
Not for publication or citation

Recurrence

Control
39·7%

30·1%

29·7%
CMF

20·4%

% ± SE

10–y gain 10·0% (SE 1·4)
Logrank 2p < 0·00001

0   5   10 years
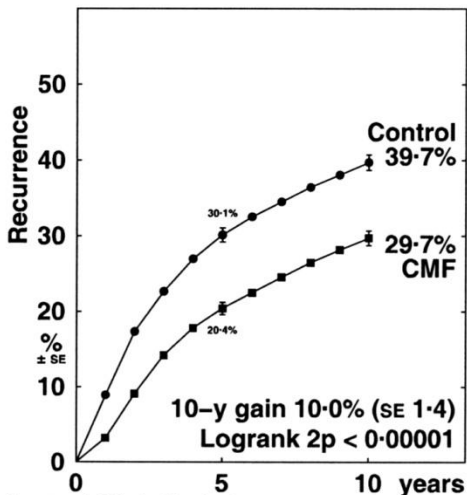
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
CMF	4·83 (549 / 11357)	2·58 (207 / 8038)	1·87 (115 / 6155)
Control	7·20 (748 / 10385)	2·93 (210 / 7158)	1·90 (100 / 5260)

Breast cancer mortality

Control
27·6%

15·3%

21·5%
CMF

11·8%

% ± S

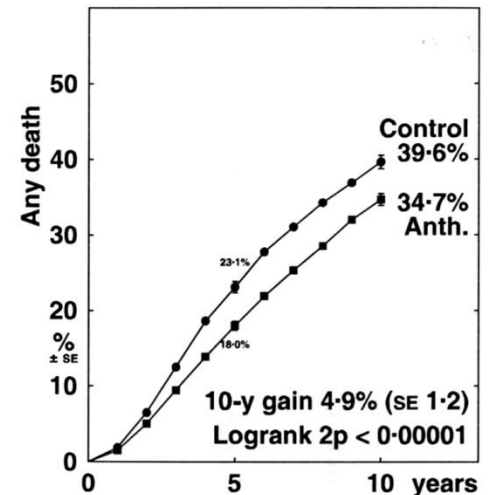10-y gain 6·0% (SE 1·3)
Logrank 2p < 0·00001

0   5   10 years

Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
CMF	2·51 se 0·14	2·42 se 0·15	1·80 se 0·16
Control	3·23 se 0·17	3·14 se 0·19	2·10 se 0·18

Any death

Control
30·6%

16·3%

26·1%
CMF

13·7%

% ± SE

10-y gain 4·6% (SE 1·3)
Logrank 2p = 0·0006

0   5   10 years
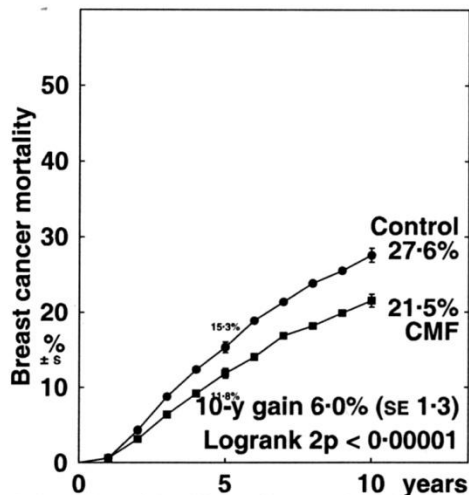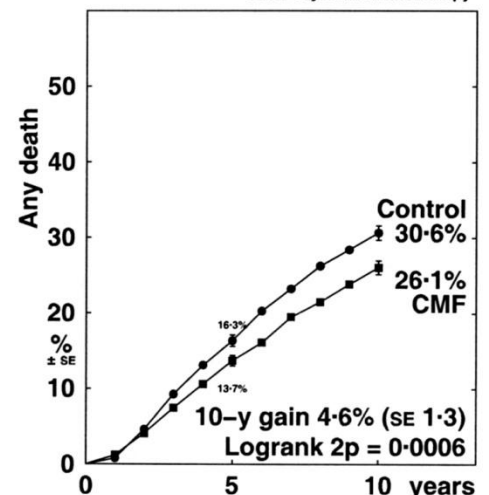
Death rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
CMF	2·93 (357 / 12167)	3·15 (286 / 9091)	3·14 (230 / 7318)
Control	3·49 (410 / 11756)	3·78 (326 / 8617)	3·39 (224 / 6612)

Fig 5A. Recurrence:
4A60C vs Standard Δ CMF

Recurrence
% ± SE

CMF 42·1%
41·0% 4AC

32·9%
32·4%

10–y gain 1·2% (SE 1·5)
Logrank 2p = 0·75

Recurrence rates (% / year) and logrank analyses			
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anthracycline	7·97 (820 / 10292)	2·86 (194 / 6795)	2·36 (100 / 4237)
CMF	8·21 (830 / 10108)	2·99 (199 / 6658)	1·87 (76 / 4054)
Rate ratio, from	0·97 se 0·05	0·91 se 0·10	1·28 se 0·17
(O–E) / V	–9·1 / 355·7	–8·5 / 92·1	10·4 / 42·3

11:11:15 18 June 2010
Not for publication or citation
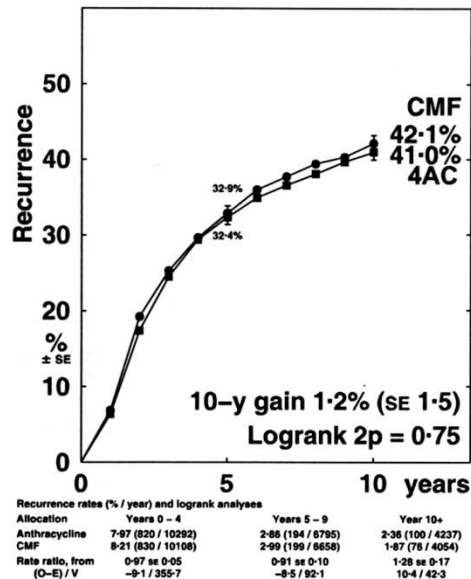
Fig 5B. Breast cancer mortality:
4A60C vs Standard Δ CMF

Breast cancer mortality
% ± SE

CMF 32·5%
31·6% 4AC

21·7%
21·2%

10–y gain 0·9% (SE 1·4)
Logrank 2p = 0·68

Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses			
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anthracycline	4·65 se 0·20	2·94 se 0·19	2·06 se 0·20
CMF	4·81 se 0·21	3·04 se 0·20	1·96 se 0·20
Rate ratio, from	0·97 se 0·06	0·97 se 0·09	1·03 se 0·15
(O–E) / V	–6·2 / 245·2	–3·7 / 111·6	1·5 / 48·9

11:11:59 18 June 2010
Not for publication or citation

Fig 5C. Any death:
4A60C vs Standard Δ CMF

Any death
% ± SE

CMF 34·6%
33·4% 4AC

22·4%
21·6%

10–y gain 1·2% (SE 1·4)
Logrank 2p = 0·55

Death rates (% / year) and logrank analyses			
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anthracycline	4·81 (551 / 11458)	3·33 (266 / 7994)	2·67 (141 / 5281)
CMF	5·00 (567 / 11351)	3·48 (274 / 7883)	2·57 (131 / 5106)
Rate ratio, from	0·97 se 0·06	0·96 se 0·09	1·01 se 0·13
(O–E) / V	–8·1 / 254·9	–5·3 / 127·6	0·8 / 64·2

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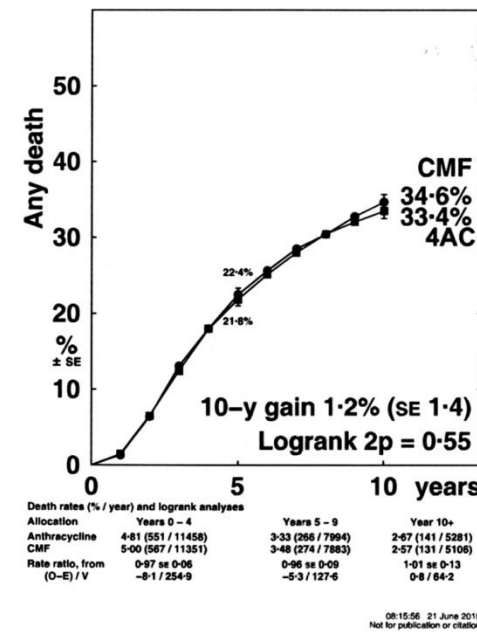
Fig 5D. Recurrence: (6FA60C, 6FE120C or other anthr.
regimen > 4A60C) vs Standard Δ CMF

Recurrence
% ± SE

6CMF 33·8%
31·2% Anthr.

25·5%
22·3%

10–y gain 2·6% (SE 1·1)
Logrank 2p = 0·003

Recurrence rates (% / year) and logrank analyses			
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anthracycline	5·05 (989 / 19575)	2·45 (238 / 9723)	1·64 (65 / 3973)
CMF	6·01 (1104 / 18377)	2·58 (238 / 9236)	1·35 (54 / 4007)
Rate ratio, from	0·85 se 0·04	1·00 se 0·10	1·13 se 0·21
(O–E) / V	–76·1 / 459·8	0·4 / 107·3	3·1 / 26·4
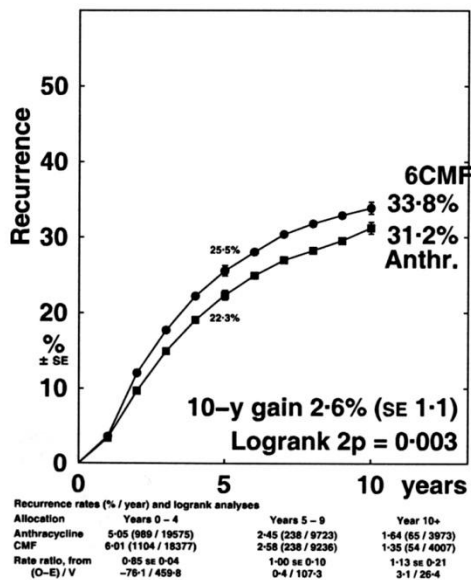
Fig 5E. Breast cancer mortality: (FA60C, FE120C or other anthr.
regimen > 4A60C) vs Standard Δ CMF

Breast cancer mortality
% ± SE

10–y gain 4·1% (SE 1·0)
Logrank 2p = 0·00001

6CMF 24·1%
20·0% Anthr.

14·5%
11·5%

Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses			
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anthracycline	2·39 se 0·11	2·08 se 0·14	0·91 se 0·14
CMF	3·06 se 0·12	2·50 se 0·15	1·11 se 0·16
Rate ratio, from	0·78 se 0·06	0·84 se 0·09	0·85 se 0·20
(O–E) / V	–63·3 / 250·4	–19·6 / 111·5	–3·4 / 20·6
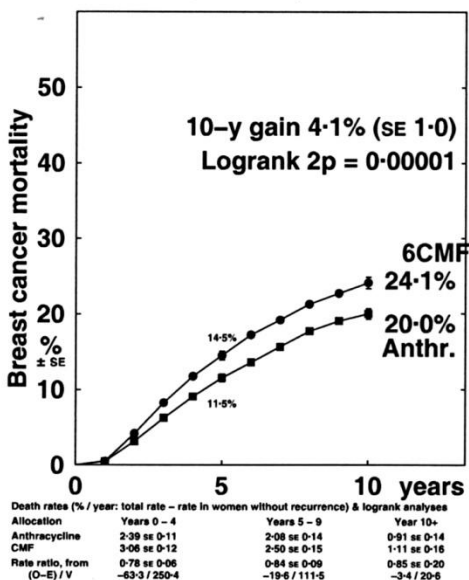
Fig 5F. Any death: (FA60C, FE120C or other anthr.
regimen > 4A60C) vs Standard Δ CMF

Any death
% ± SE

CMF 27·1%
23·2% Anthr.

15·8%
12·8%

10–y gain 3·9% (SE 1·1)
Logrank 2p = 0·0001

Death rates (% / year) and logrank analyses			
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anthracycline	2·67 (561 / 20977)	2·60 (290 / 11151)	1·99 (90 / 4528)
CMF	3·36 (669 / 19894)	2·99 (319 / 10661)	1·92 (87 / 4521)
Rate ratio, from	0·79 se 0·05	0·87 se 0·08	1·07 se 0·16
(O–E) / V	–65·7 / 279·2	–18·5 / 137·8	2·6 / 41·0

Fig 2A. Recurrence: Taxane+anthr. regimen (eg, 4AC/4EC) vs SAME anthracycline-based regimen

SAME anth 34·7%
30·3% Tax + anth
8-y gain 4·4% (SE 1·0)
Logrank 2p = 0·00001

Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Year 5+
Tax + anth	5·51 (1280 / 23249)	3·10 (413 / 13343)
SAME anth	6·43 (1239 / 19259)	3·62 (381 / 10534)
Rate ratio, from	0·85 se 0·04	0·85 se 0·07
(O–E) / V	−89·2 / 555·1	−29·6 / 182·1

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Fig 2B. Breast death: Taxane+anthr. regimen(eg, 4AC/4EC) vs SAME anthracycline-based regimen
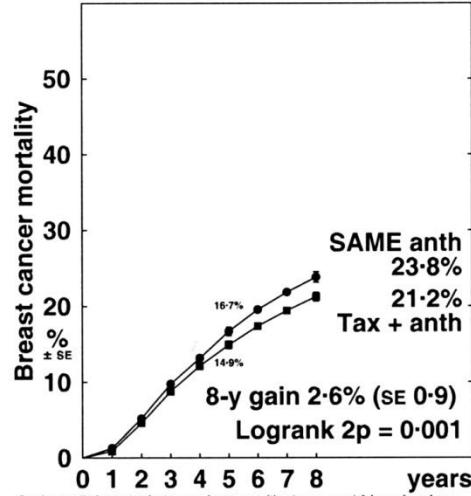
SAME anth 23·8%
21·2% Tax + anth
8-y gain 2·6% (SE 0·9)
Logrank 2p = 0·001

Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Year 5+
Tax + anth	3·21 se 0·11	2·48 se 0·13
SAME anth	3·58 se 0·13	3·06 se 0·16
Rate ratio, from	0·88 se 0·05	0·84 se 0·07
(O–E) / V	−42·8 / 347·5	−30·7 / 172·2

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Not for publication or citation

**Fig 2C. Any death: Taxane+anthr. regimen (eg, 4AC/4EC) vs SAME anthracycline-based regimen**

SAME anth 26·6%
23·6% Tax + anth
8-y gain 2·9% (SE 0·9)
Logrank 2p = 0·0006
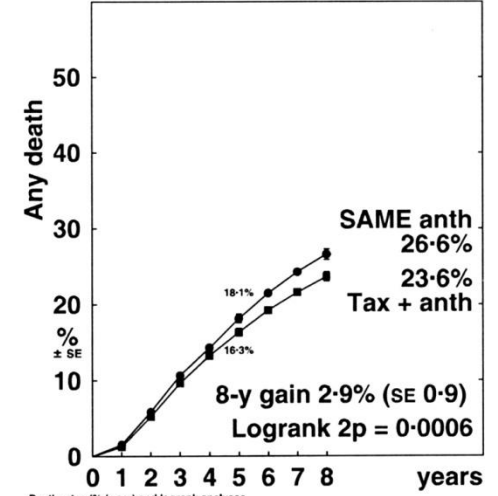
Death rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Year 5+
Tax + anth	3·55 (881 / 24821)	3·09 (465 / 15061)
SAME anth	3·93 (819 / 20850)	3·76 (458 / 12178)
Rate ratio, from	0·89 se 0·05	0·83 se 0·06
(O–E) / V	−44·7 / 385·0	−38·9 / 213·2

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Not for publication or citation

Fig 2D. Recurrence: Taxane+anthracycline-based regimen vs STRONGER anthracycline-based regimen

5-y gain 2·8% (SE 0·6)
Logrank 2p < 0·00001
STRONGER anth 22·0%
19·2% Tax + anth
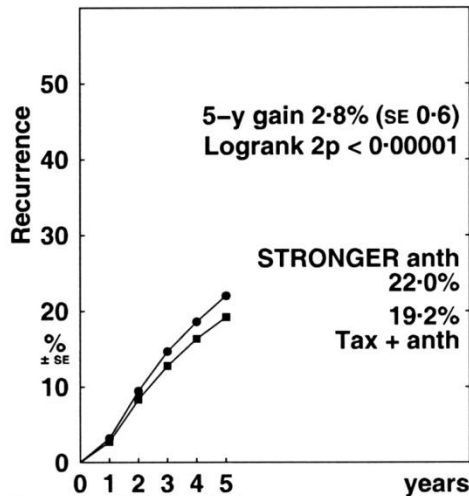
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Year 5+
Tax + anth	4·37 (2607 / 59665)	3·01 (153 / 5082)

Fig 2E. Breast death: Taxane+anthracycline-based regimen vs STRONGER anthracycline-based regimen

5-y gain 1·3% (SE 0·4)
Logrank 2p = 0·003
STRONGER anth 11·5%
10·2% Tax + anth
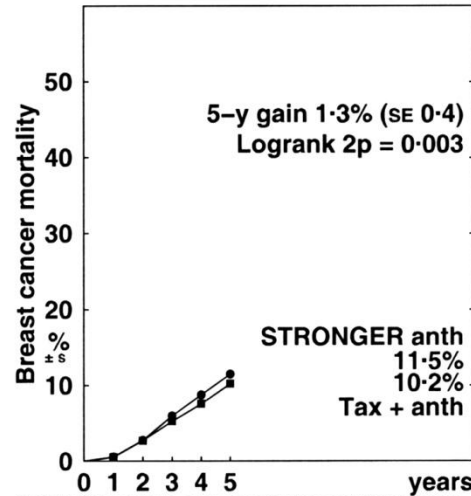
Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Year 5+
Tax + anth	2·01 se 0·06	2·37 se 0·20

Fig 2F. Any death: Taxane+anthracycline-based regimen vs STRONGER anthracycline-based regimen

5-y gain 1·1% (SE 0·5)
Logrank 2p = 0·02
STRONGER anth 12·4%
11·3% Tax + anth
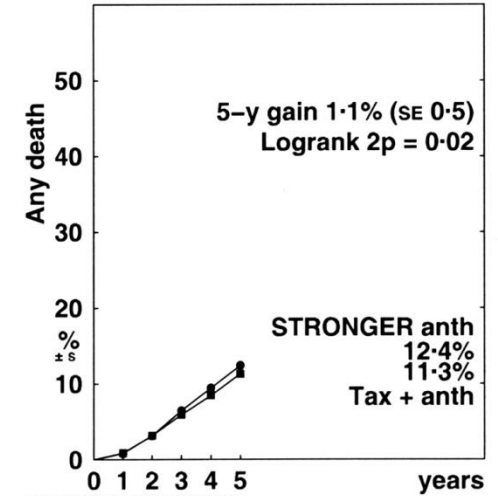
Death rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Year 5+
Tax + anth	2·24 (1326 / 59104)	2·85 (161 / 5658)

6

Oxford overwiew 2010 EBCTCG : Taxan regiment vs no treatment: Age <50

	Recurrence	Breast cancer death
CMF vs no treat	0.56 (0.05)	0.68 (0.05)
Anthr. vs CMF	0.84 (0.05)	0.81 (0.05)
Taxan vs Anthr.	0.84 (0.04)	0.86 (0.05)
Taksan vs no chem Multiplying 3 RR	0.38 (0.07) 2p<0.00001	0.46 (0.08) 2p>0.00001

Oxford overwiew 2010

- Proprotionaly reductions of recurence and breast cancer mortality given by taxane or anthracycyline regiments were mostly independent of

- Age

- Nodal status

- Tumor size

- Differntiation (high vs intermediate)

- ER status

Nothigham prognostic Index (NPI)

- NPI = (0,2x S) + N + G
- S = size of primary tumor in cm
- N = number of metastatic nodes 0=1; 1-3 = 2; >3= 3
- G = grade I =1; II= 2; III=3

NPI	5 survival
>/=2,0 do </=2,4	93%
>2,4 do </=3,4	85%
>3,4 do </=5,4	70%
> 5,4	50%

Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham Prognostic Index in primary breast cancer. Breast Cancer Research & Treatment 1992;22(3):207-19

Adjuvant! Online
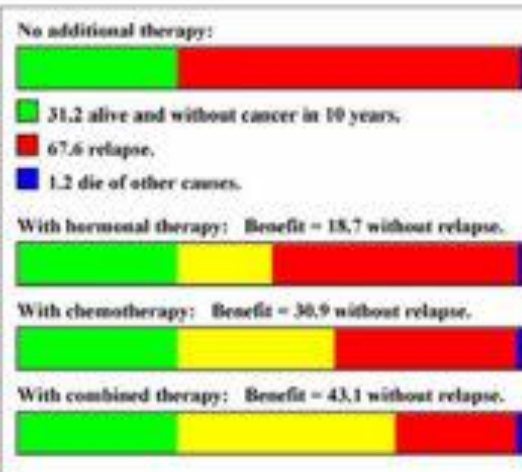
Table 1. Commercially Available Genomic Assays for the Prediction of Clinical Outcome in Patients with Breast Cancer.*

Variable	MammaPrint	Oncotype DX	Theros	MapQuant Dx
Provider	Agendia	Genomic Health	Biotheranostics	Ipsogen
Type of assay	70-Gene assay	21-Gene recurrence score	2-Gene ratio of HOXB13 to IL17R (H/I) and molecular-grade index	Genomic grade
Type of tissue sample	Fresh or frozen	Formalin-fixed, paraffin-embedded	Formalin-fixed, paraffin-embedded	Fresh or frozen
Technique	DNA microarrays	Q-RT-PCR	Q-RT-PCR	DNA microarrays
Centrally certified laboratory†	Yes	Yes	Yes	Yes
Indication	To aid in prognostic prediction in patients <61 yr of age with stage I or II, node-negative disease with a tumor size of ≤5 cm	To predict the risk of recurrence in patients with ER-positive, node-negative disease treated with tamoxifen; to identify patients with a low risk of recurrence who may not need adjuvant chemotherapy	To stratify ER-positive patients into groups with a predicted low risk or high risk of recurrence and a predicted good or poor response to endocrine therapy	To restratify grade 2 tumors into low-risk grade 1 or high-risk grade 3 tumors, specifically for invasive, primary, ER-positive grade 2 tumors
Level of evidence (I–V)‡	III	II	III	III
FDA clearance	Yes	No	No	No
Availability	Europe and United States	Europe and United States	United States	Europe

* ER denotes estrogen receptor, FDA Food and Drug Administration, and Q-RT-PCR quantitative reverse-transcriptase–polymerase chain reaction.
† Laboratories were certified according to the criteria of the Clinical Laboratory Improvement Amendments or by the International Organization for Standardization.
‡ Levels of evidence are measured on a scale ranging from I (strongest) to V (weakest).[54]

Oncotype DX 21 Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

$$RS = + 0.47 \times \text{HER2 Group Score}$$
$$- 0.34 \times \text{ER Group Score}$$
$$+ 1.04 \times \text{Proliferation Group Score}$$
$$+ 0.10 \times \text{Invasion Group Score}$$
$$+ 0.05 \times \text{CD68}$$
$$- 0.08 \times \text{GSTM1}$$
$$- 0.07 \times \text{BAG1}$$

GSTM1   **BAG1**

INVASION
Stromolysin 3
Cathepsin L2

CD68

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

Category	RS (0 – 100)
Low risk	RS < 18
Intermed risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

Paik S, NEJM 351(27):2817, 2004
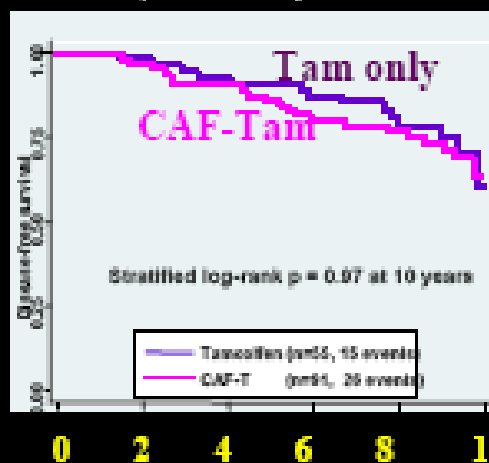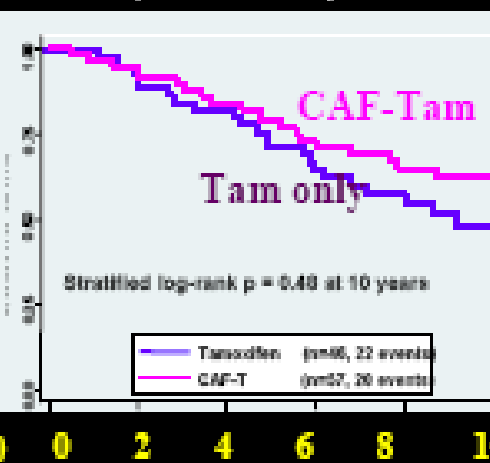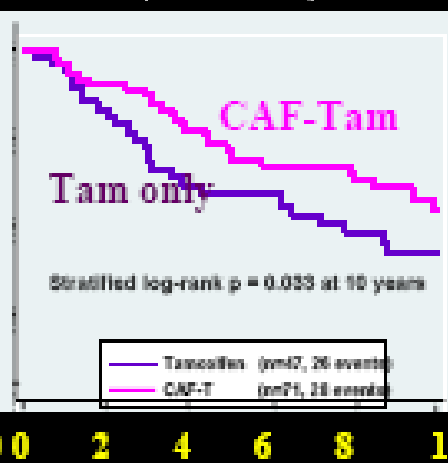
Intristic molecular clasyfication of breast cancer

Intristic type	IHC	Proliferation and grade	Treatment
Basal - like	Mostly triple negative	High Ki67 High grade	Chemotherapy
Luminal A	Mostly ER+	Low Ki67 Low grade	Hormonal treatment
Luminal B	Mosttly ER+	Often high Ki67 High grade	Less/ unresponsive to hormonal treatment Resposive to chemotherapy
HER2 +	HER2 overexpressed	High Ki 67	AntiHer2 treatment

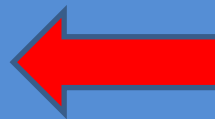**TNM + Grade** **+** **Size of the tumor +pN** → **Nothingam Prognostic Index**

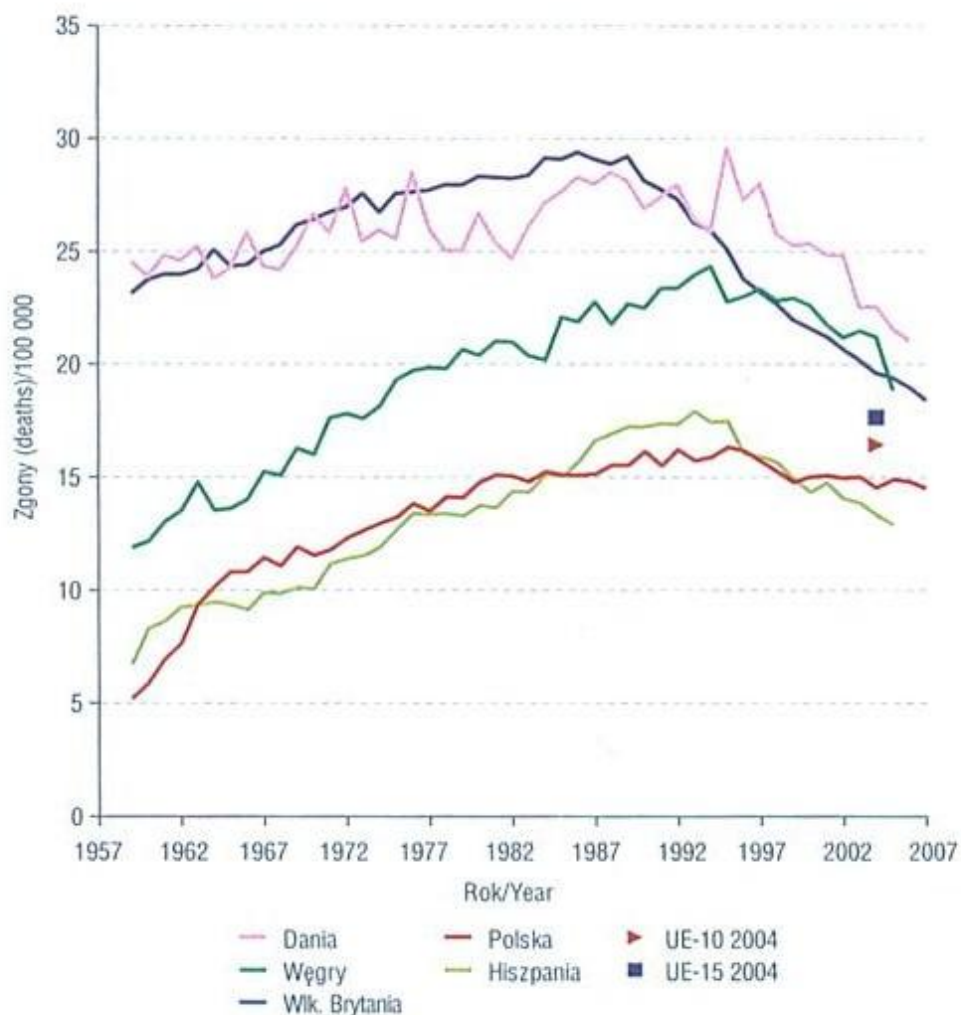**+**

ER

↓

Clinical practice ← **HER2 and LVI ?** **+** **Adjuvant!Online**

Rysunek 4.9. Trendy umieralności na nowotwory złośliwe piersi żeńskiej w wybranych krajach Europy w latach 1959–2007

Figure 4.9. *Mortality trends for female breast cancer in selected European countries in years 1959–2007*

Adjuvant Therapy in Breast Cancer: The Future

- Clinical features, stage and biology all contribute to risk of recurrence!
- Endocrine therapy critical in ER+ breast cancer
- In chemotherapy-sensitive breast cancers, anthracycline and taxanes both add to disease control
- Many patients don't need chemo!
- Trastuzumab significantly reduces breast cancer recurrence and death in HER2+
- Ongoing prospective trials are integrating traditional and novel markers of risk to better define tailored options for early-stage breast cancer