

Ruolo della chemioterapia adiuvante nelle pazienti con EBC e positività dei recettori ormonali: inefficacia o necessità di schemi diversi?

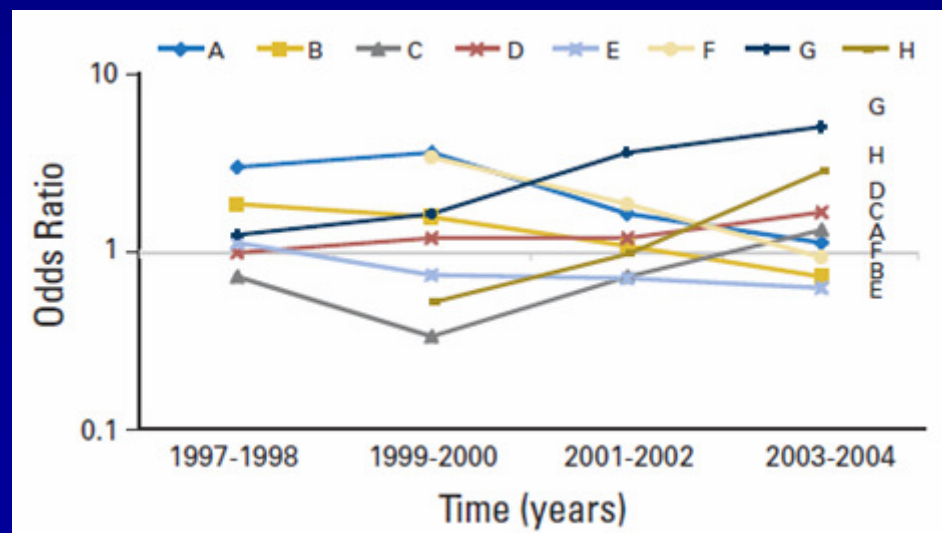
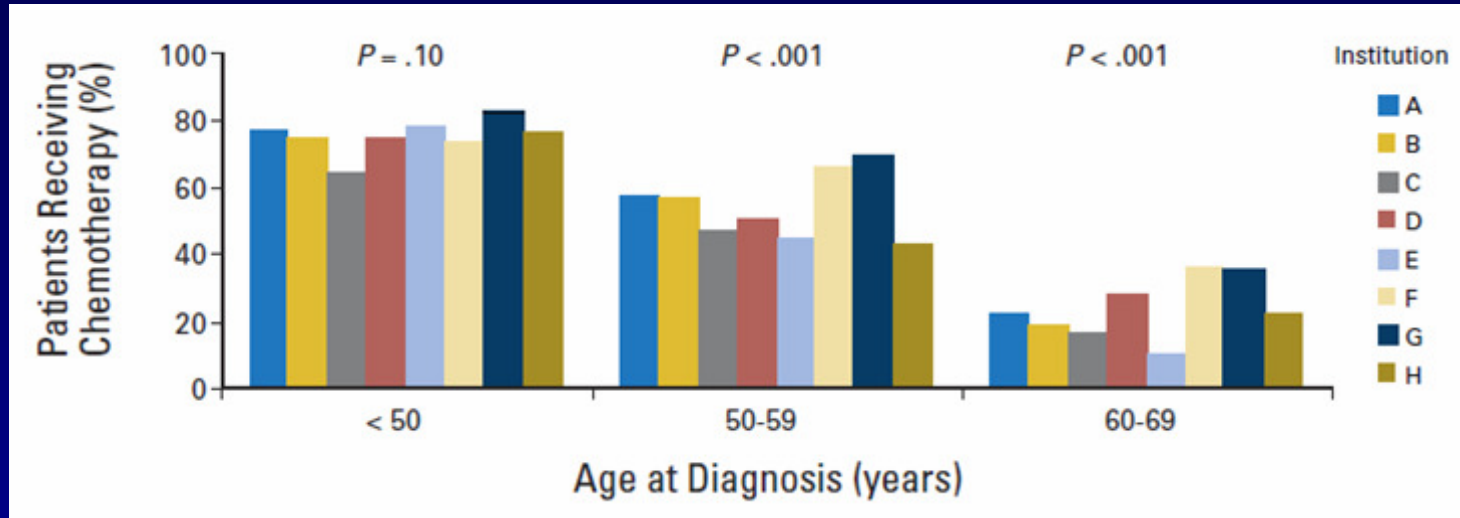
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Meldola**

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PER LO STUDI E LA CURA
DEI TUMORI

Use of CT in ER+ early breast cancer

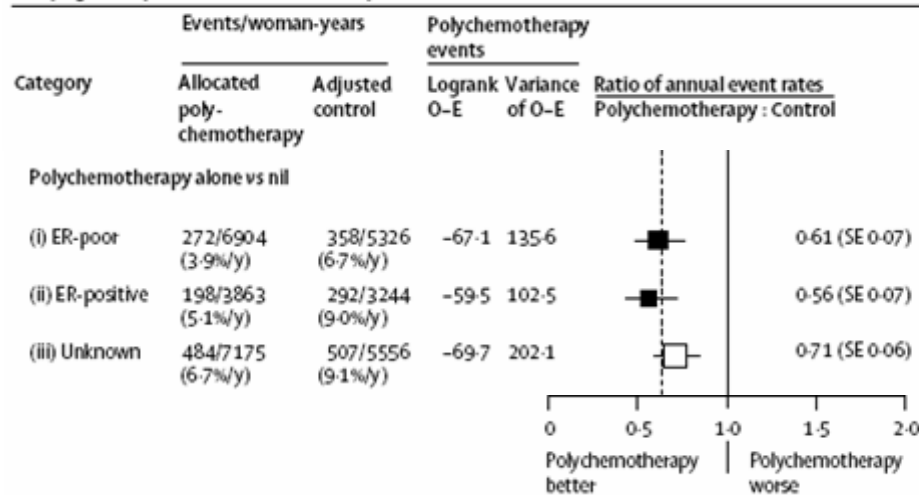
- Frequency of chemotherapy use for HR+, N- breast cancer from 1997 to 2004 at eight National Comprehensive Cancer Network institutions



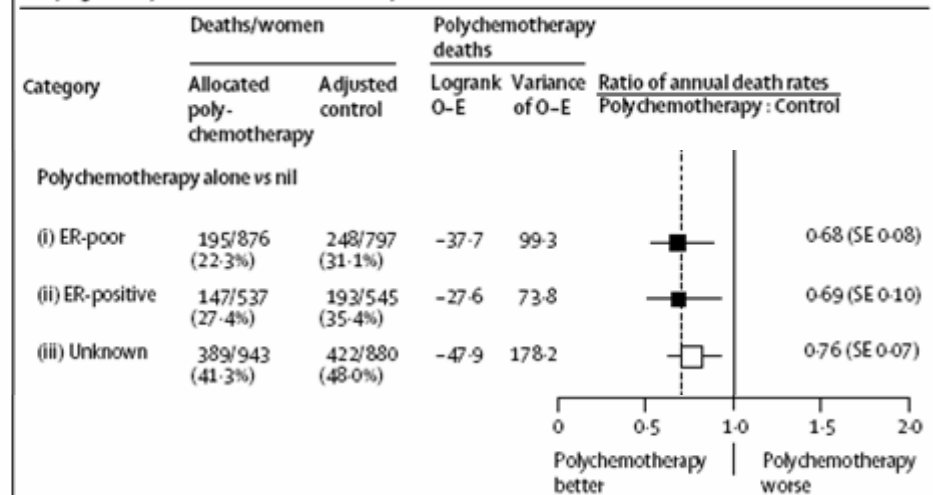
Adjuvant CT vs nil in ER+ and ER- early breast cancer

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 2005; 365: 1687–1717

Entry age <50 years: recurrence/woman-years



Entry age <50 years: breast cancer mortality/women



CT vs ET in ER+ patients' cohorts

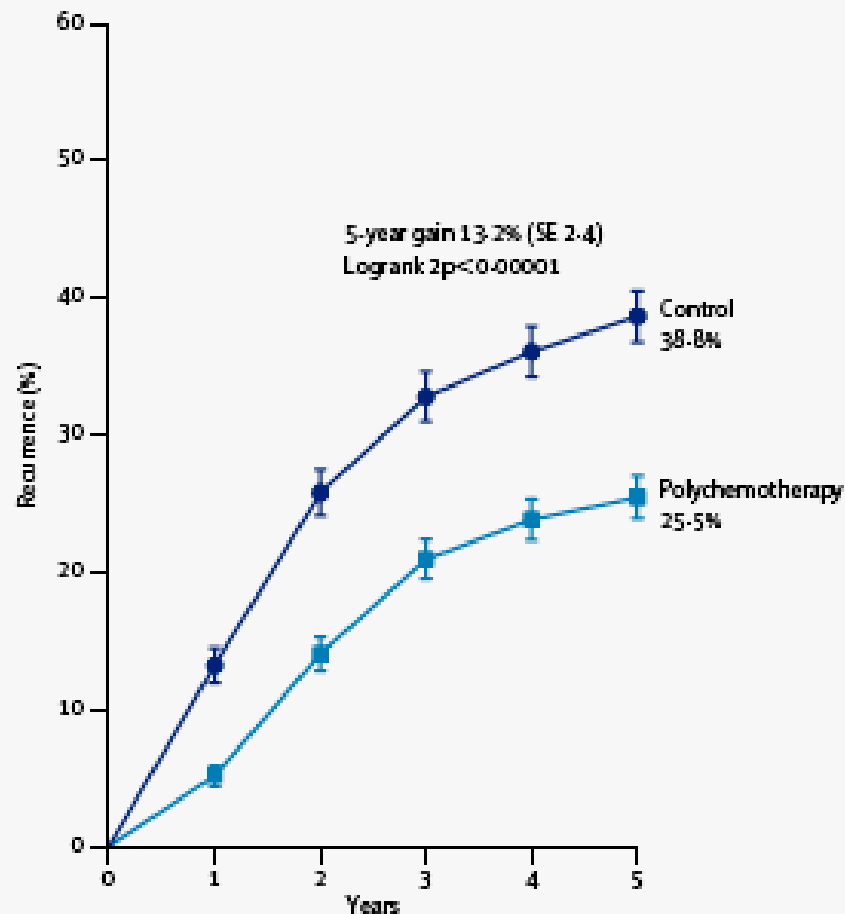
Study	Treatment	Patients	Results in ER+ cohorts
ZEBRA (N = 1,640) Kaufmann M et al. Eur J Cancer 2003	CMF x 6 G x 2 years	N+; ER+/-	No difference
IBCSG VIII (N = 1,063) Karlsson P et al. Ann Oncol 2011	CMF x 6 G x 24 months (CMF x 6 → G x 18 months)	N-; ER+/-	No difference
Scottish (N = 332) Thomson CS et al. Breast 2002	CMF x 6 to 8 OA (oophorectomy)	N+	No difference
Scandinavian (N = 732) Ejlertsen B et al. J Clin Oncol 2006	CMF x 9 OA (RT)	N+; ER+	No difference
TABLE (N = 600) Schmid et al. Anticancer Res 2002	CMF x 6 Leuprorelin x 2 yrs	N+; ER+	No difference
GROCTA (N = 504) Boccardo F et al. Ann N Y Acad Sci 1993	Tam x 5 years CMF x 6 → E x 4 (CMF x 6 → E x 4 + Tam x 5 yrs)	N+, ER+,	Tam > CT for DFS and OS;
GABG (N = 331) Kaufmann et al. J Clin Oncol 2006	CMF iv Tam x 2 years	N+1-3, ER+	No difference overall; CMF > Tam for DFS and OS in pts <50 yrs; TAM > CMF for DFS in pts ≥50 yrs.
ABCSG (N = 1,034) Jakesz R et al. J Clin Oncol 2002	CMF x 6 G x 3 years + Tam x 5 years	N+/-, ER+	CMF < G + Tam for DFS
GROCTA 02 (N = 244) Boccardo F et al. J Clin Oncol 2000	OA (surgery, RT, or G x 2 years) + Tam 30 mg x 5 years CMF x 6	N+/-, ER+	No difference
FASG 02 (N = 776) Namer M et al. An Oncol 2006	Tam x 3 years FEC50 x 6 (FEC50 x 6 + Tam x 3 years No treatment)	N+, ER+/-, postmenop	Tam > FEC for DFS
France (N = 162) Roché H et al. Proc ASCO 1996	FAC x 6 OA (surgery or RT) + Tam 30 mg x 2 years	N+, ER+	No difference
FASG 06 (N = 333) An Oncol 2006	Tam 30 mg + triptorelin x 3 years (n = 164) FEC x 6 (n = 169)	N+, ER+	No difference

G = goserelin; OA = ovarian ablation

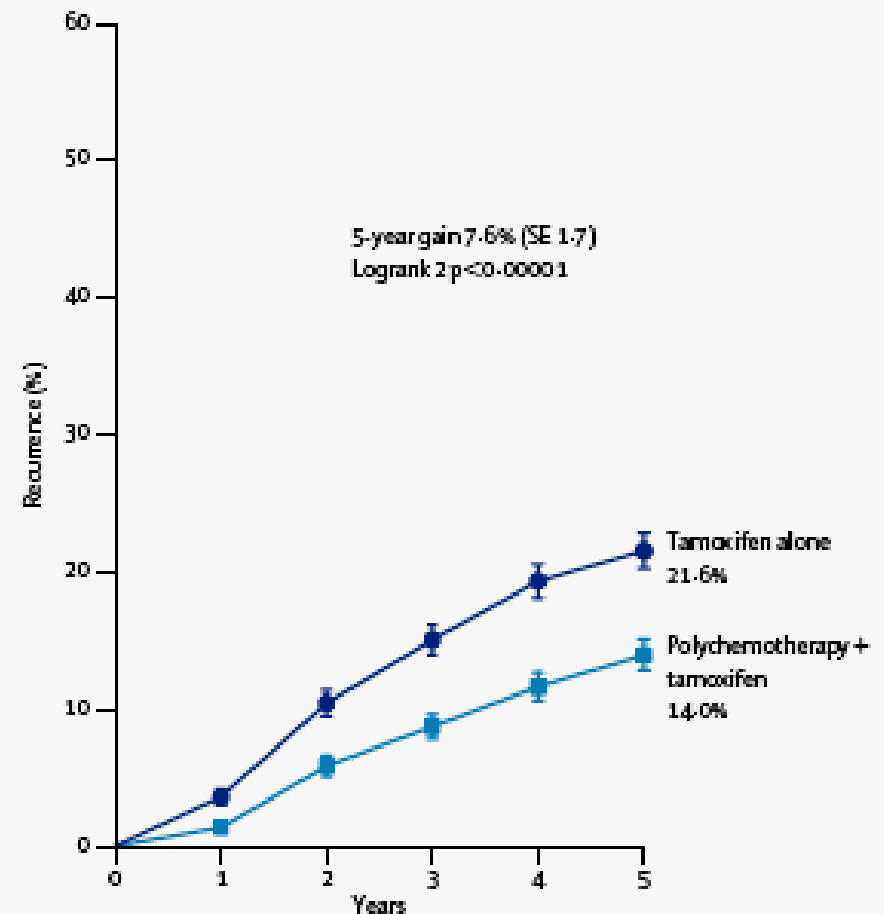
Polychemotherapy versus not in ER-poor disease or in tamoxifen-treated ER-positive disease: 15-year probabilities of recurrence. Age < 50 years.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 2005; 365: 1687–1717

Entry age < 50 years, ER-poor: polychemotherapy vs not
(1757 women: 20% node-positive)



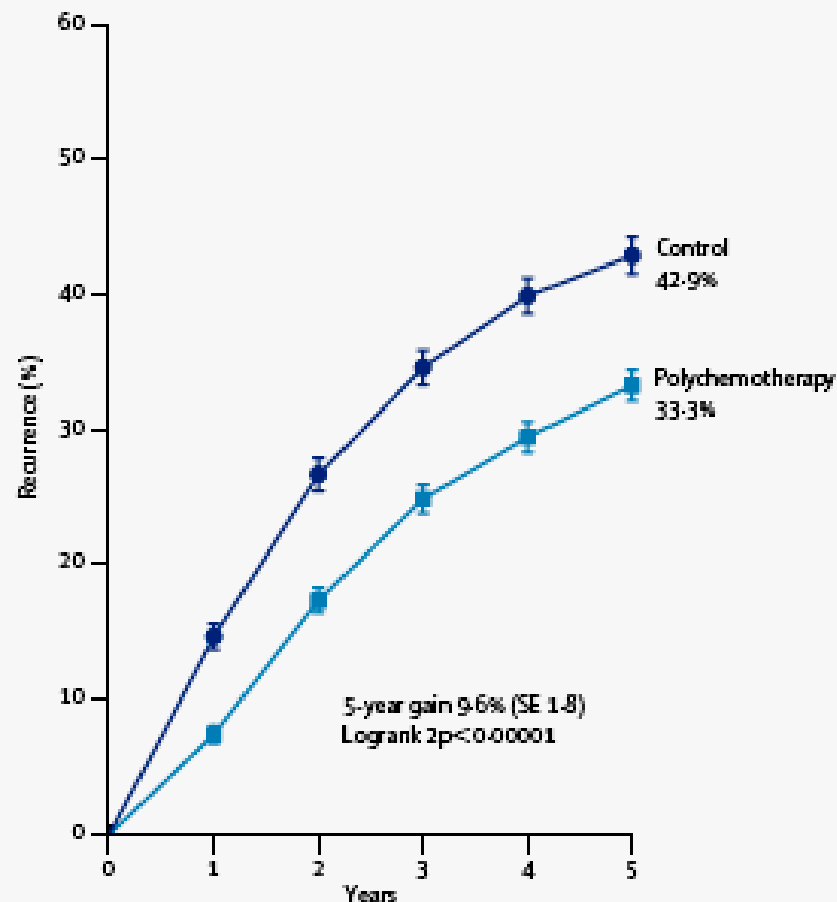
Entry age < 50 years, ER-positive: polychemotherapy + tamoxifen vs tamoxifen alone
(2254 women: 34% node-positive)



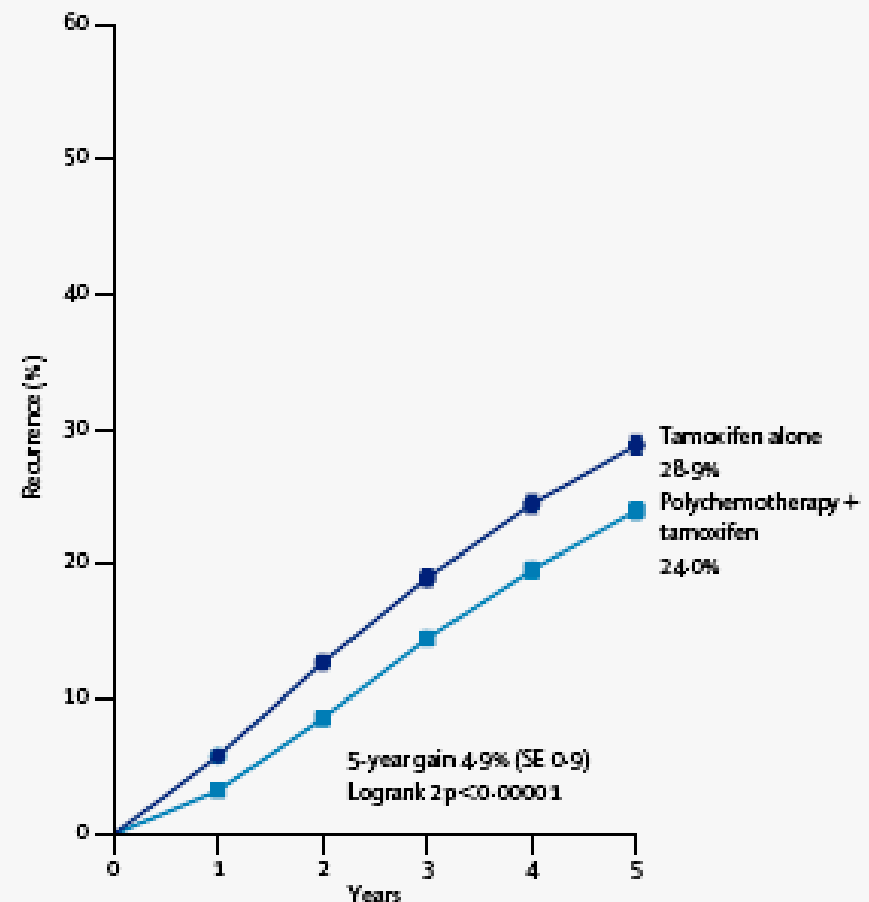
Polychemotherapy versus not in ER-poor disease or in tamoxifen-treated ER-positive disease: 15-year probabilities of recurrence. Age 50-69 years.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 2005; 365: 1687–1717

Entry age 50–69 years, ER-poor: polychemotherapy vs not
(4071 women: 66% node-positive)

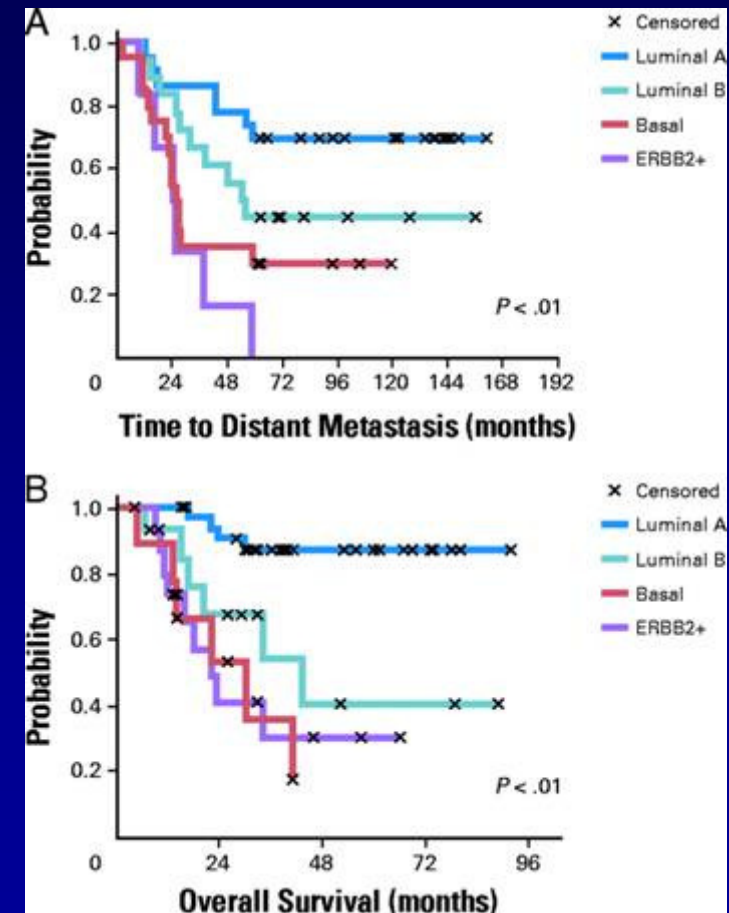
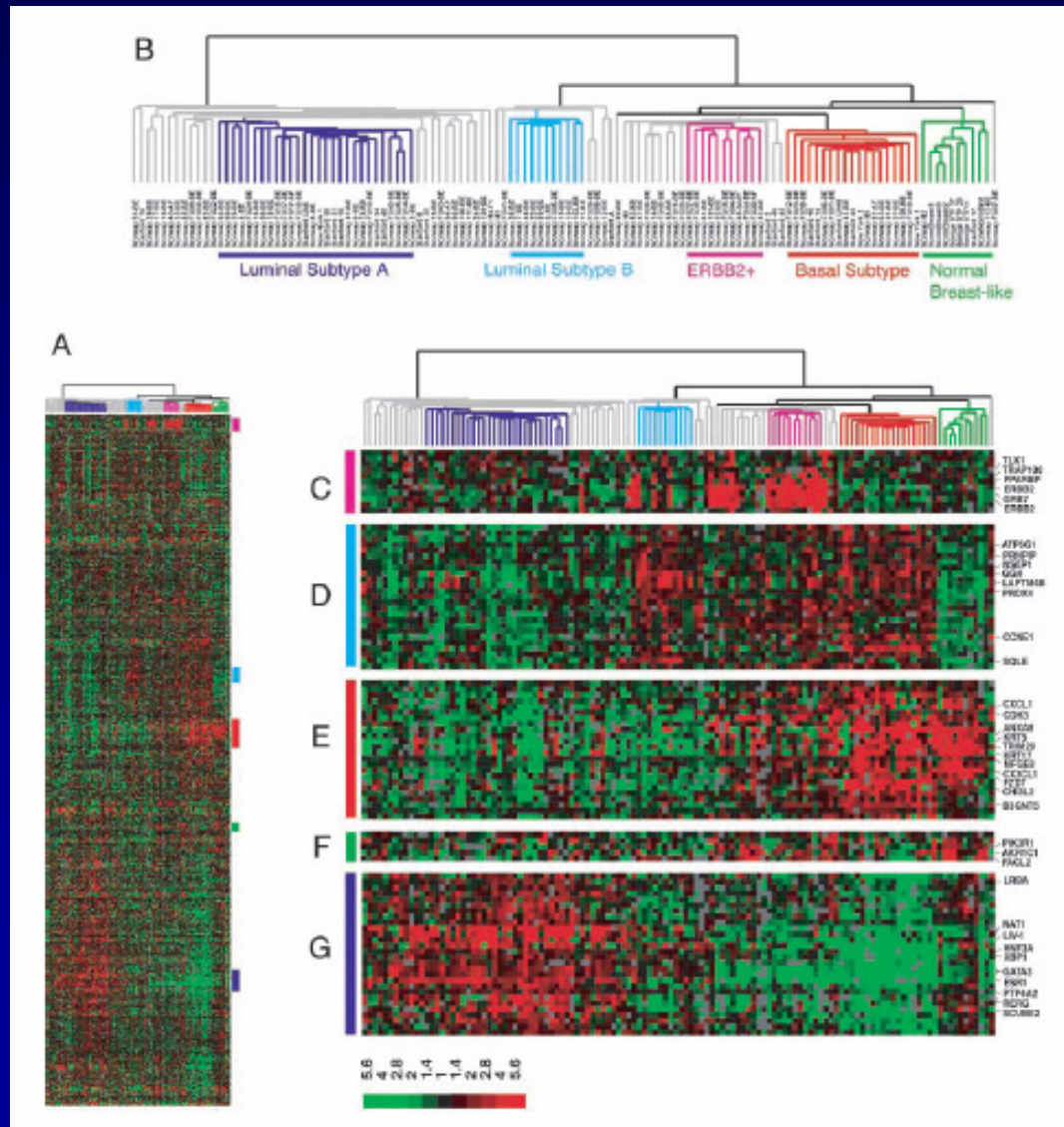


Entry age 50–69 years, ER-positive: polychemotherapy + tamoxifen vs tamoxifen alone
(11 333 women: 73% node-positive)



Breast cancer subtypes

Brenton, J. D. et al. J Clin Oncol; 23:7350-7360 2005

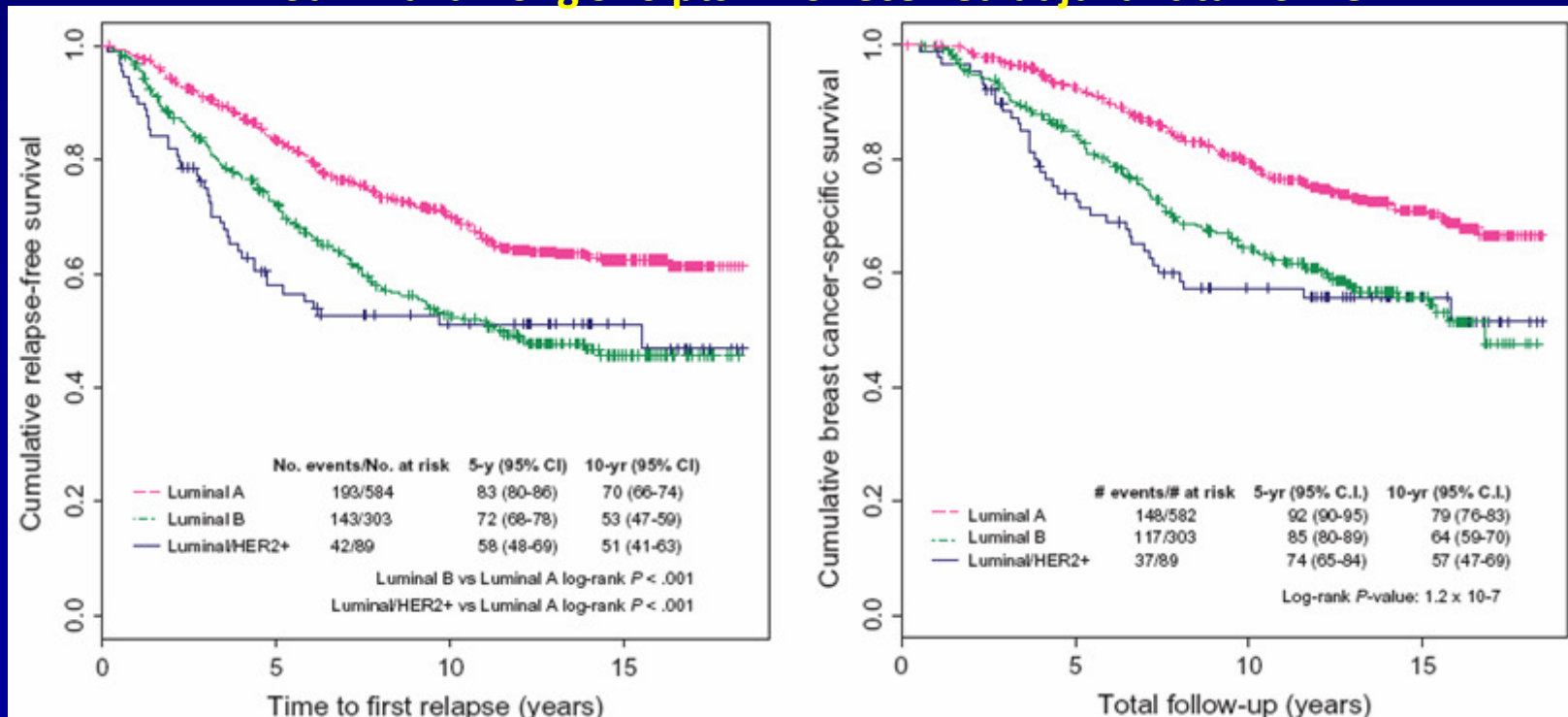


Identifying luminal B cancers

Cheang MCU. et al. J Natl Cancer Inst 2009; 101: 736 – 750

- Immunohistochemistry (IHC) assay to distinguish luminal B from luminal A tumors
- Training cohort of 357 patients subtyped by gene expression profile; ER, PgR, HER2, and Ki67 determined by IHC. best **Ki67 index cut point** to distinguish luminal B from luminal A: **13.25%**
- **Luminal A: ER+, HER2-, low Ki-67**
- **Luminal B: ER+, HER2-, high Ki-67**
- **Luminal HER2+: ER+, HER2+**
- Independent prognostic value in a series of 4046 breast cancers

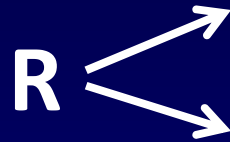
Survival among 976 pts who received adjuvant tamoxifen



Role of estrogen receptor levels

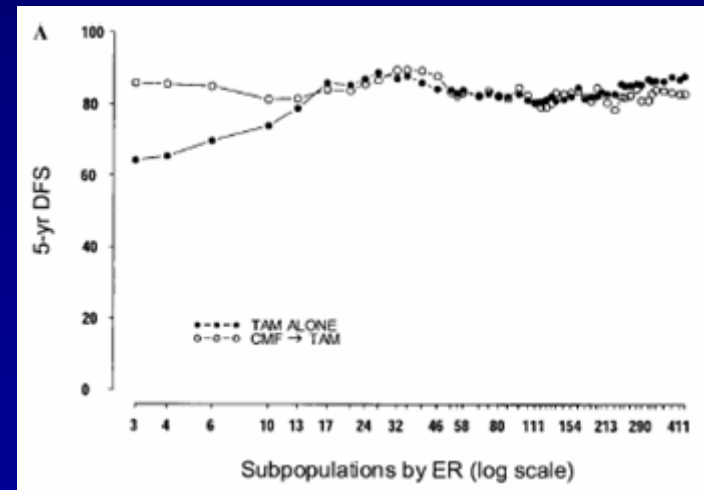
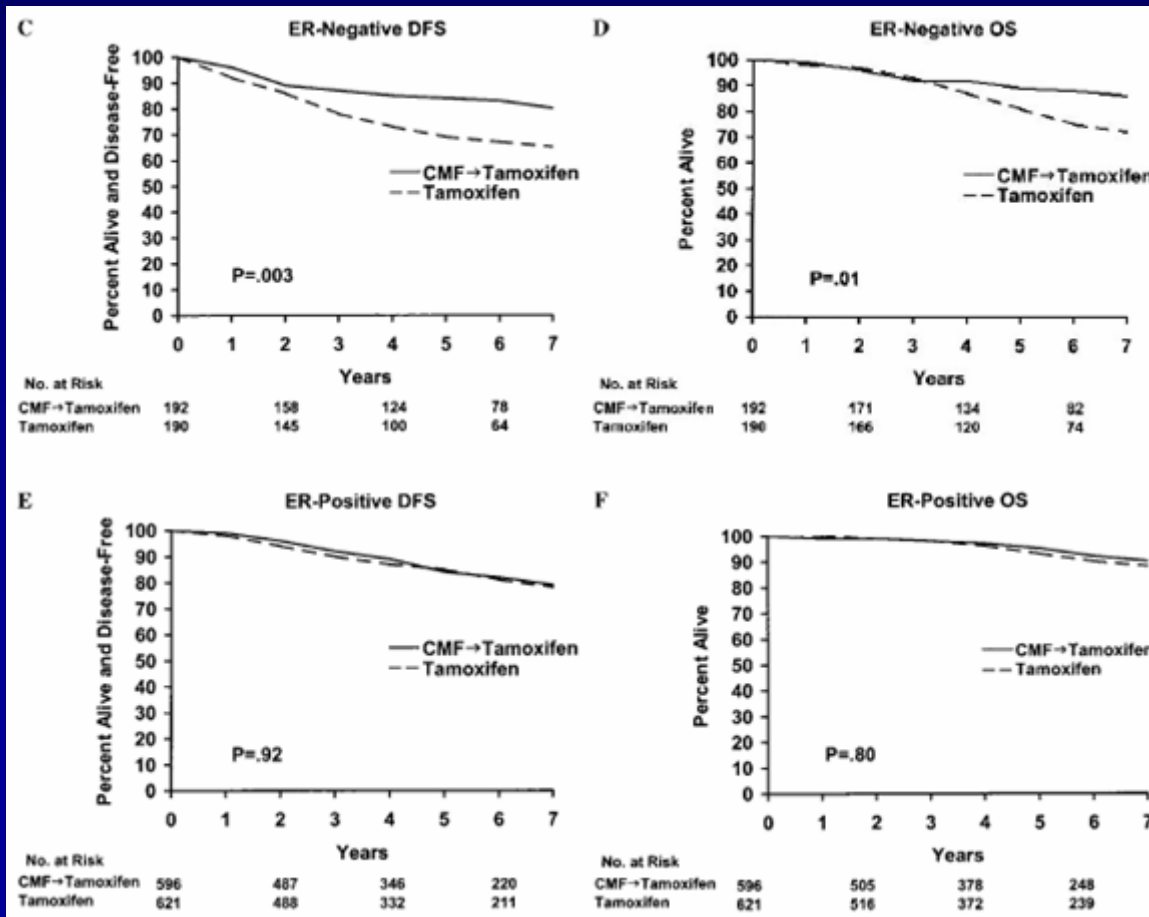
Adjuvant chemotherapy for postmenopausal pts with N- tumors: IBCSG IX

- 1669 postmenopausal pts
- N-
- ER+ (73%) or ER- (23%)



Tam x 60 months

Classical CMF x 3 → Tam x 57 months

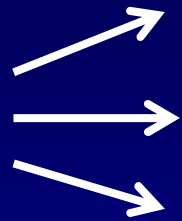


International Breast Cancer Study Group (IBCSG).
J Natl Cancer Inst 2002;94: 1054–65

Adjuvant chemotherapy for postmenopausal women with ER+ tumors: SWOG-8814 INT-0100

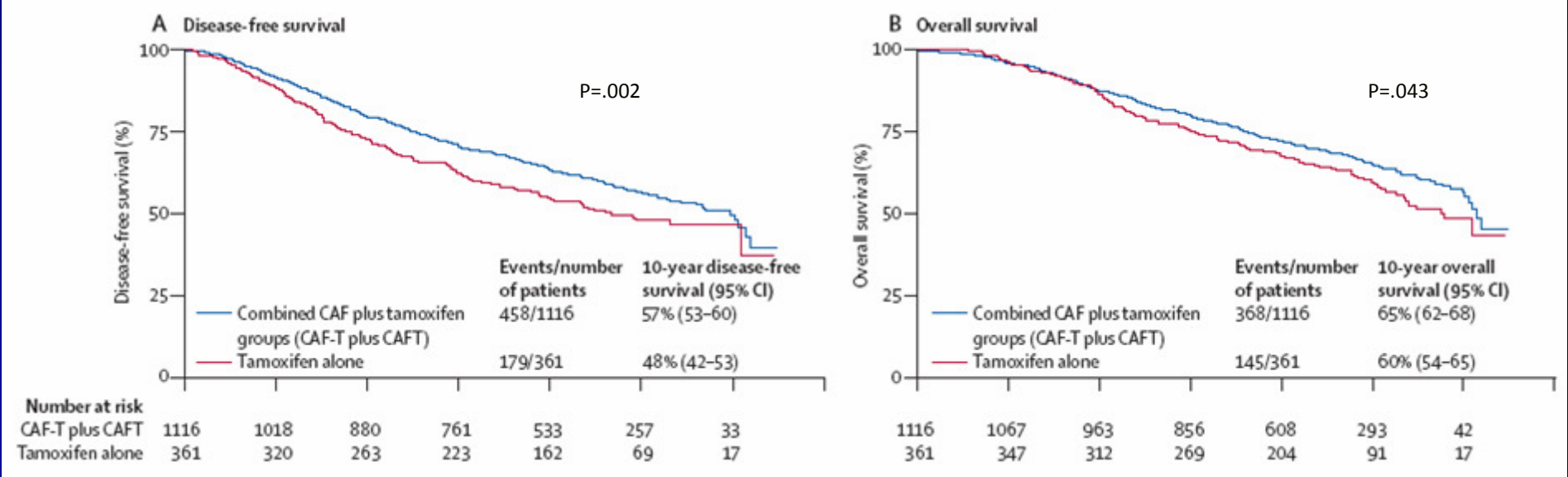
Albain KS, et al. Lancet 2009; 374: 2055-63

R



- Tamoxifen x 5 years
- CAF x 6 + Tam x 5 years
- CAF x 6 → Tam x 5 years

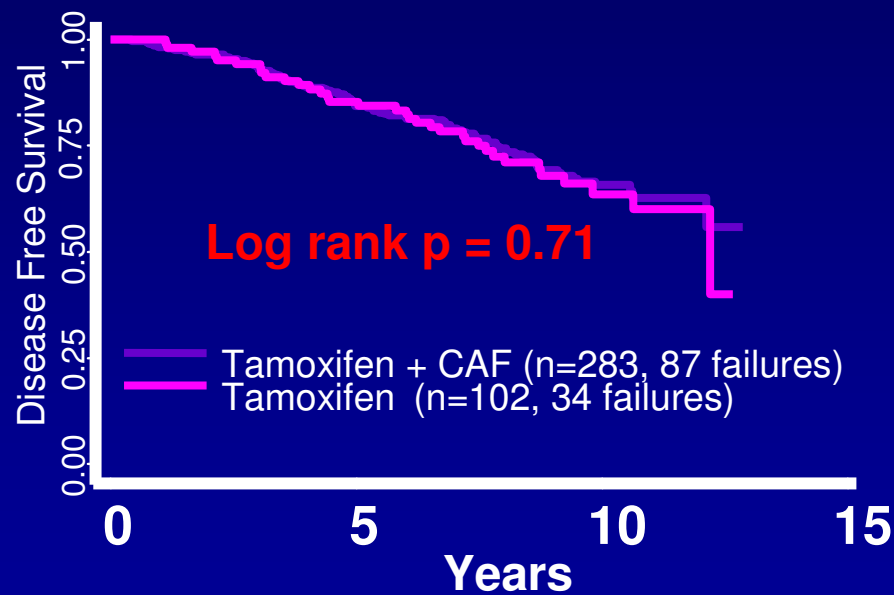
- 1558 postmenopausal women
- Node-positive,
- hormone receptor-positive



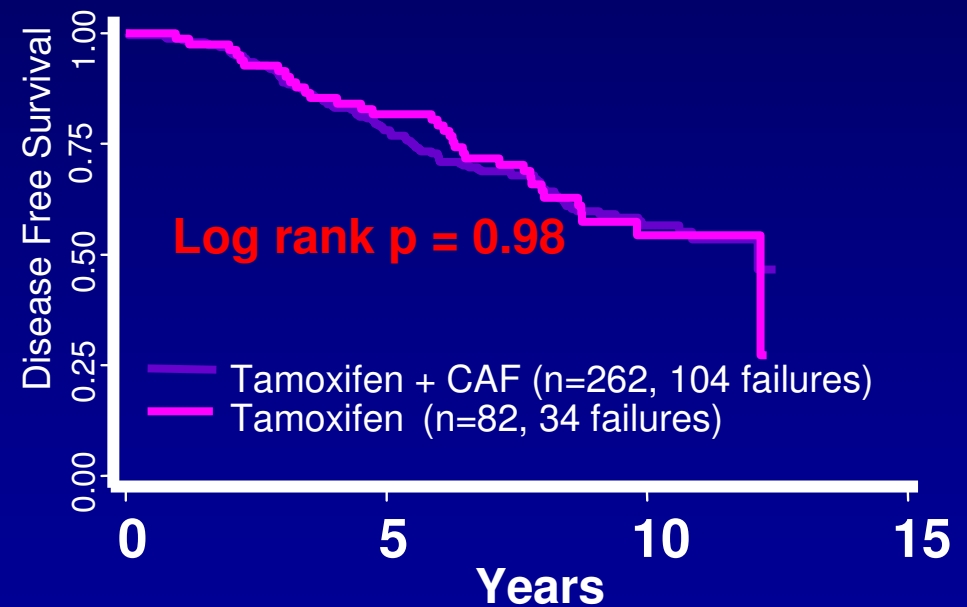
Adjuvant chemotherapy for postmenopausal women with ER+ tumors: SWOG-8814 INT-0100

Albain KS, et al. PSABCS 2004

HER2(-), N 1-3(+)



ER highly expressed



Adjuvant chemotherapy for premenopausal pts with N+, ER+ tumors: IBCSG 11-93

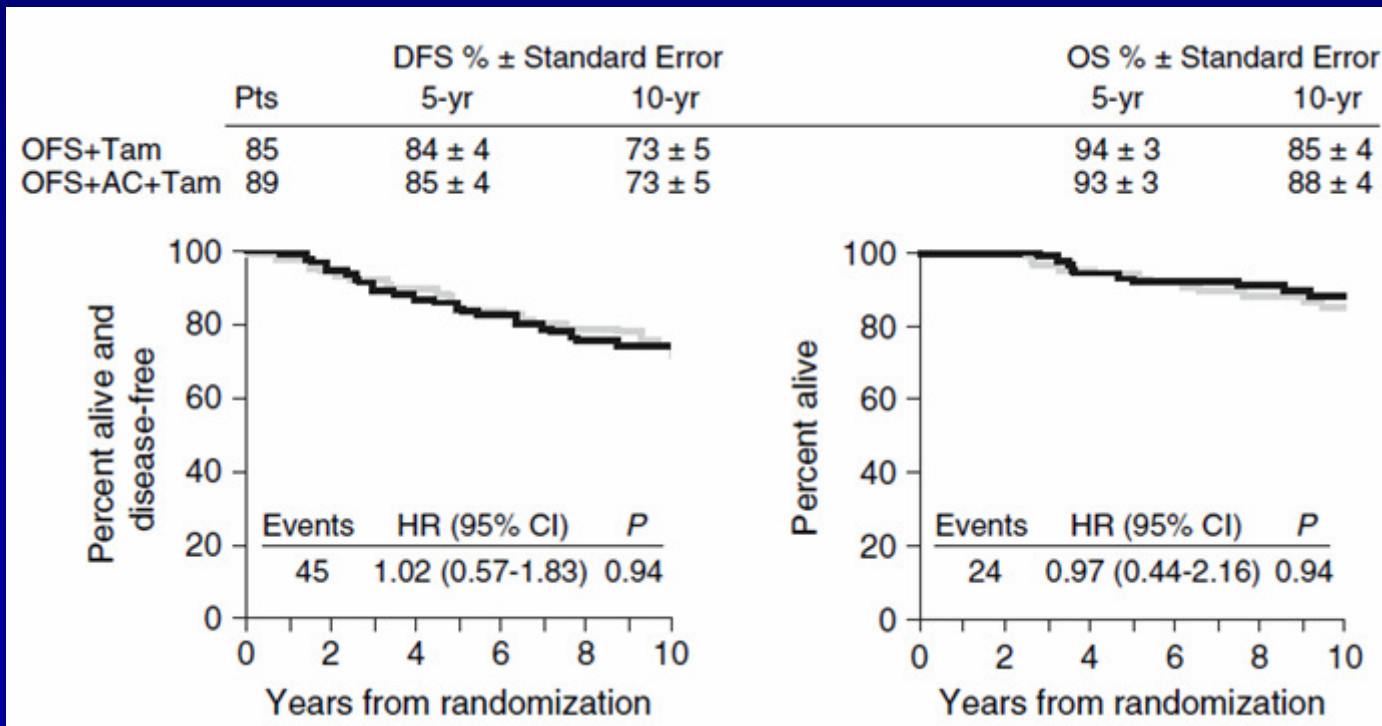
- 174 premenopausal pts, ER+ N+ (planned sample size 760), suitable for ET

R

Ovarian function suppression (OFS) (GnRHa/Surg/RT)

OFS + A₆₀C₆₀₀ x 4

- No evidence of benefit from CT, but highly unpowered

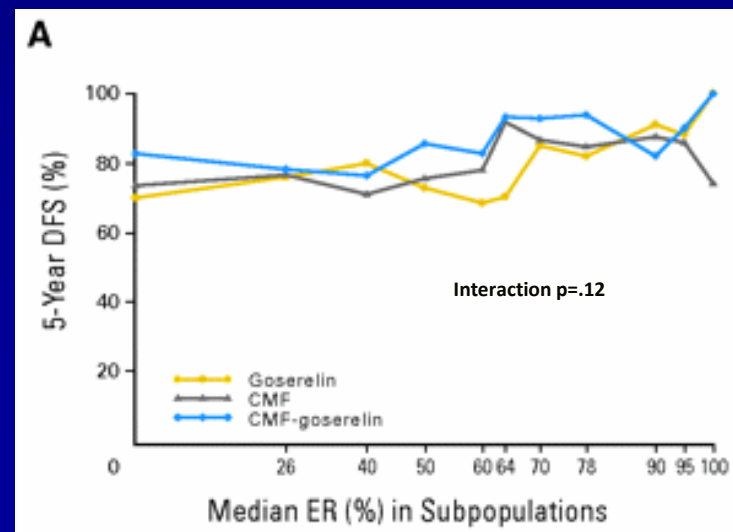
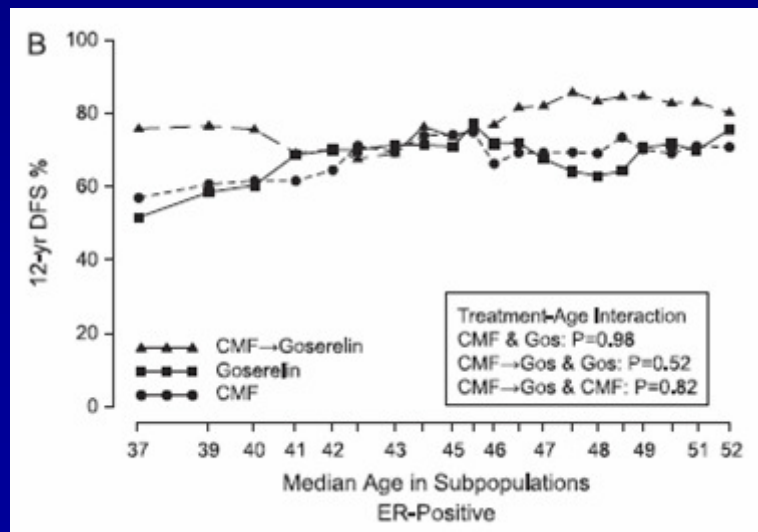
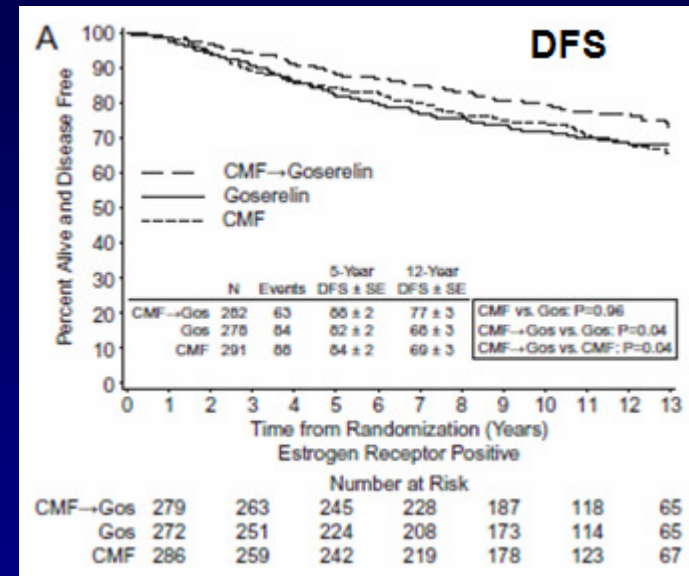


Role of amenorrhea

Adjuvant chemotherapy for premenopausal pts with N- tumors: IBCSG VIII

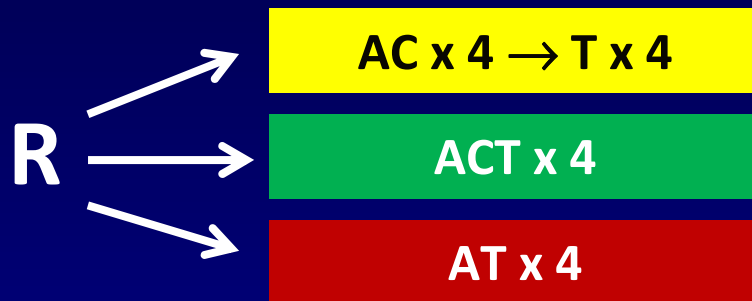


- 1063 pre-perimenopausal pts, N-
- 80% ER+, 19% ER-, 1% unknown
- **ER+ cohort: ↑ DFS with CMF → goserelin**
- Benefit largely confined to *younger pts (< 40 ys)*
- CMF → goserelin clearly *prolonged amenorrhea*



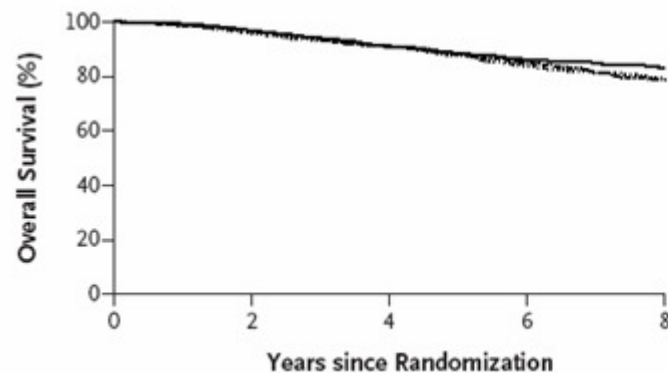
Adjuvant chemotherapy and amenorrhea: NSABP B-30 trial

Swain SM, et al. N Engl J Med 2010; 362: 2053-65

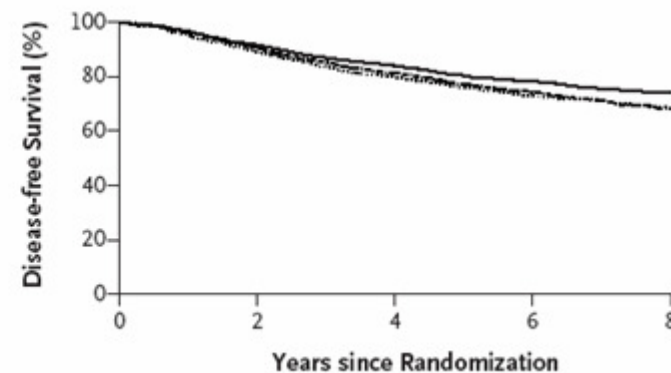


- 5351 pts overall, N+
- Prospective assessment of menstrual history in 1885 premenopausal pts

	No. of Patients	No. of Events	Hazard Ratio	P Value
— Sequential ACT	1753	240	0.86 vs. concurrent ACT	0.09
			0.83 vs. doxorubicin-docetaxel	0.03
— Doxorubicin-docetaxel	1753	285		
- - - Concurrent ACT	1758	278	0.96 vs. doxorubicin-docetaxel	0.67



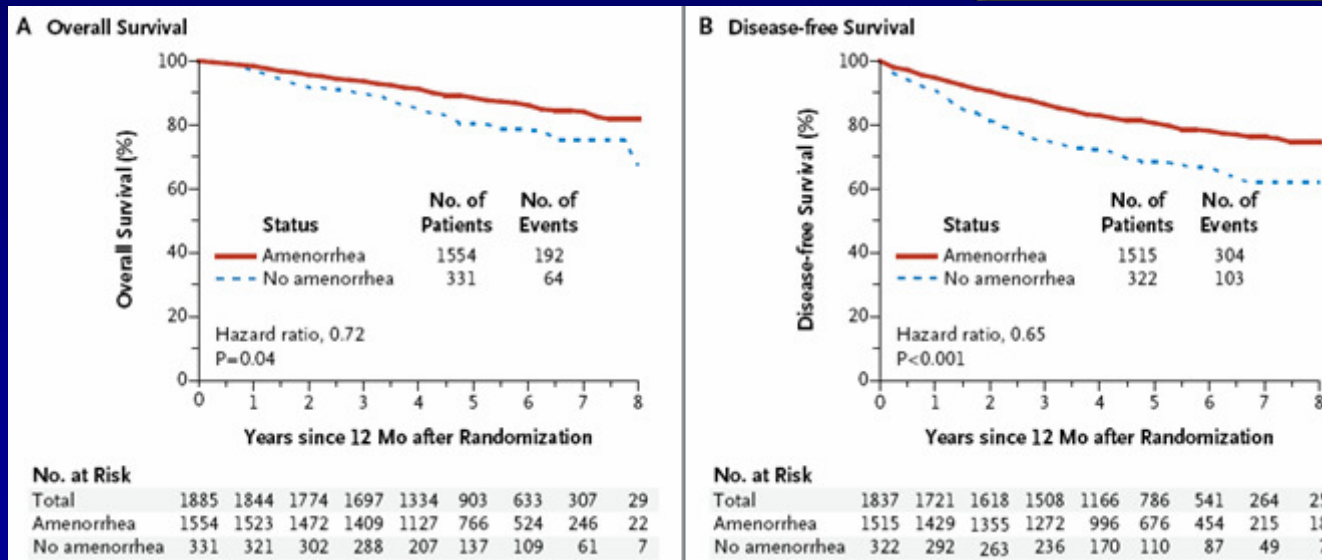
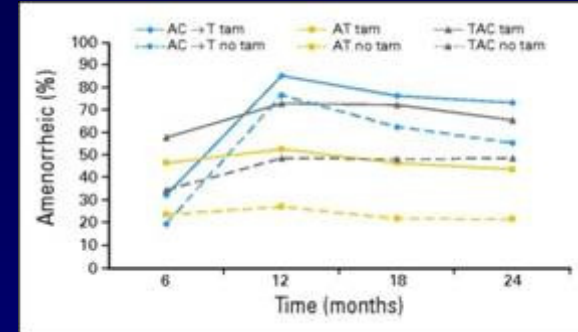
	No. of Patients	No. of Events	Hazard Ratio	P Value
— Sequential ACT	1753	388	0.83 vs. concurrent ACT	0.01
			0.80 vs. doxorubicin-docetaxel	0.001
— Doxorubicin-docetaxel	1753	468		
- - - Concurrent ACT	1758	457	0.96 vs. doxorubicin-docetaxel	0.58



Impact of amenorrhea: NSABP B-30 trial

Swain SM, et al. N Engl J Med 2010; 363: 2268-70

- 12-month landmark analysis (including women with at least 1 year of follow-up)
- Differences are not related to drug doses



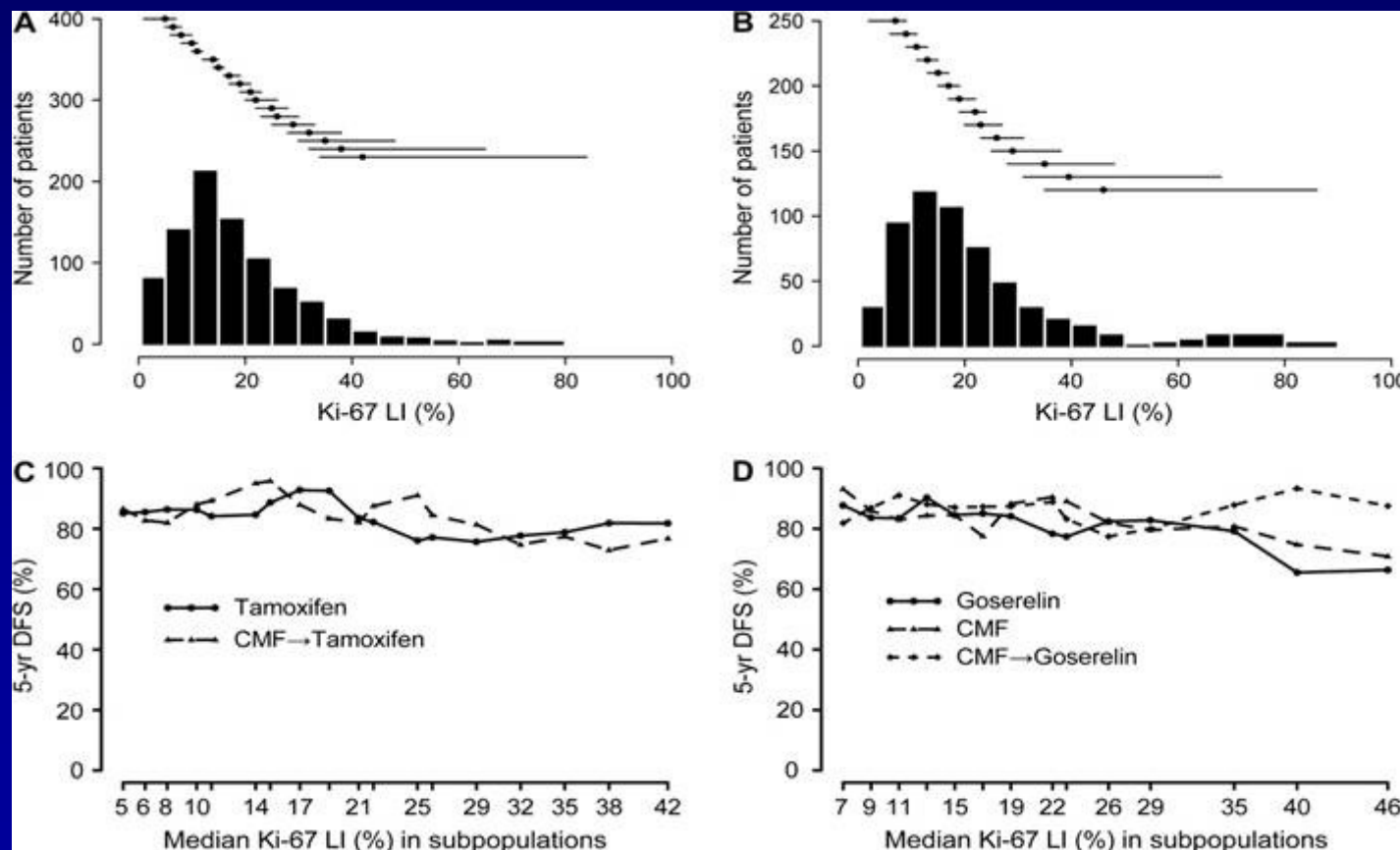
ER status	OS-HR (amenorrhea vs not)	p	DFS-HR (amenorrhea vs not)	p
ER+	0.52	.002	0.51	<.001
ER-	1.08	.76	0.96	.85

Role of proliferation

Adjuvant chemotherapy for ER+ tumors: impact of Ki-67. IBCSG VII and 12-93

Viale, G. et al. J. Natl. Cancer Inst. 2008 100:207-212

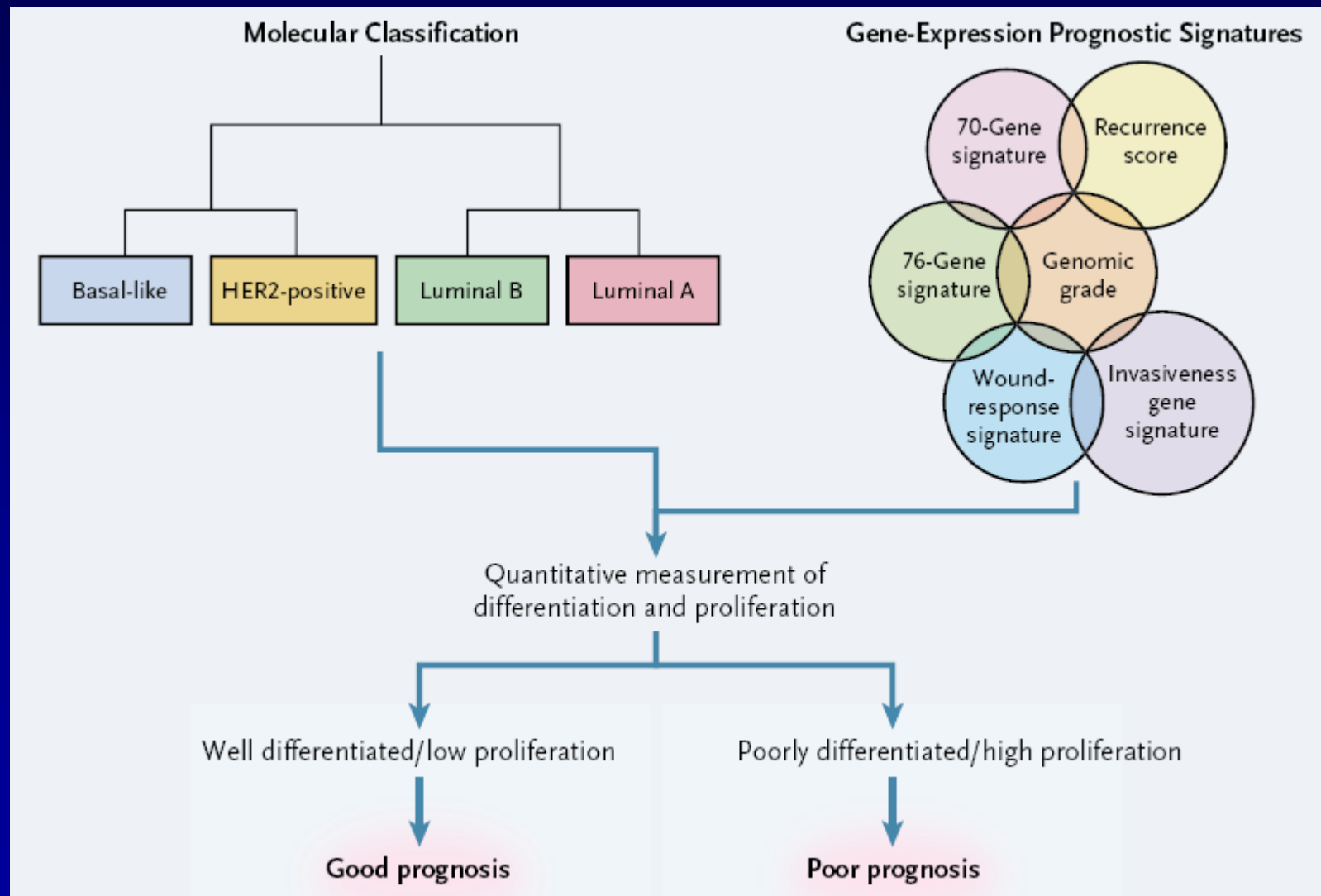
- Centrally reviewed tumor samples of 1924 pts from:
 - IBCSG Trial VIII (premenopause): goserelin x 2 y, CMF x 6, CMF → goserelin x 2y
 - IBCSG Trial IX (postmenopause): Tam, CMF x 3 → Tam
- No interaction between Ki-67 and treatment
- Ki-67 independent prognostic factor but not predictive factor



Multigene assays to predict
adjuvant chemotherapy benefit
over endocrine therapy

Gene expression signatures in breast cancer

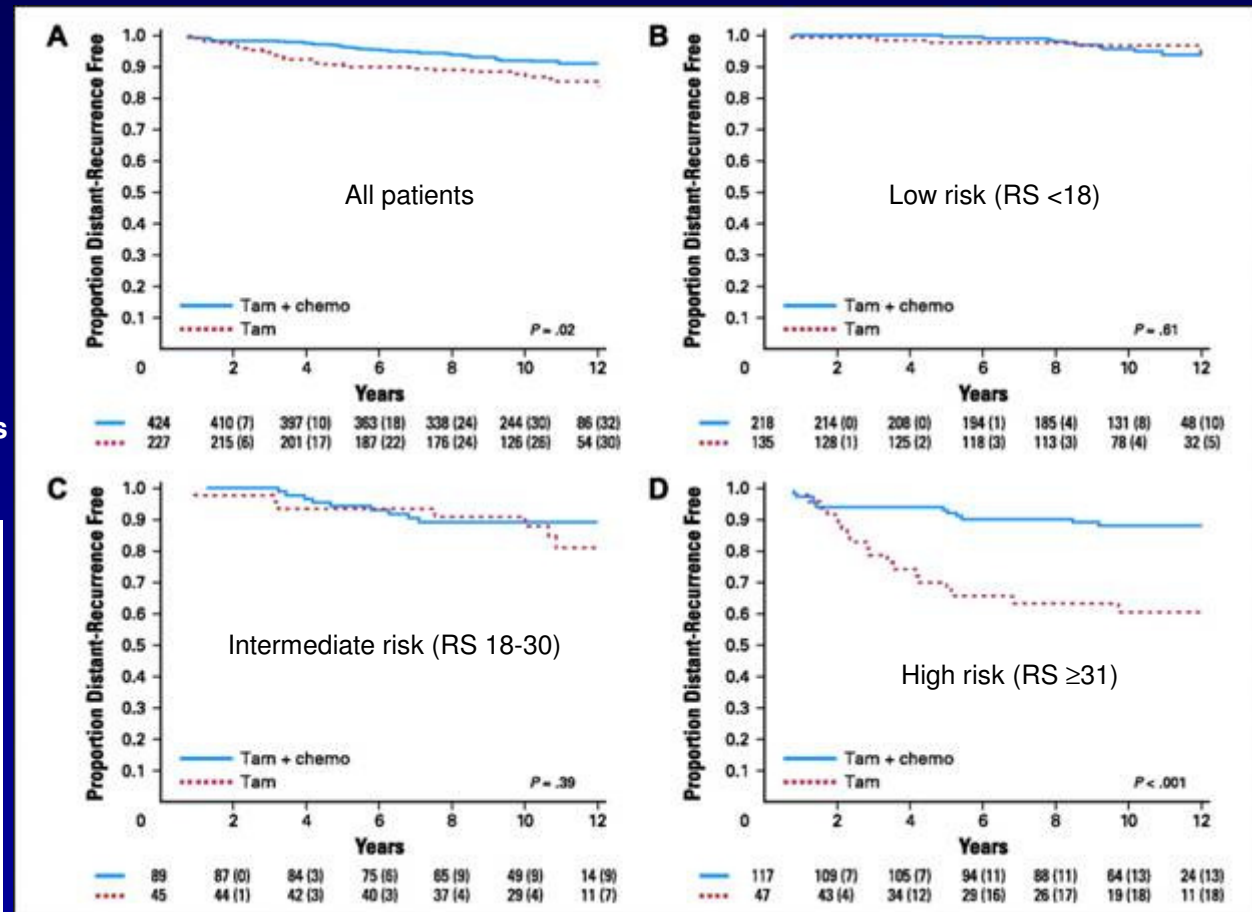
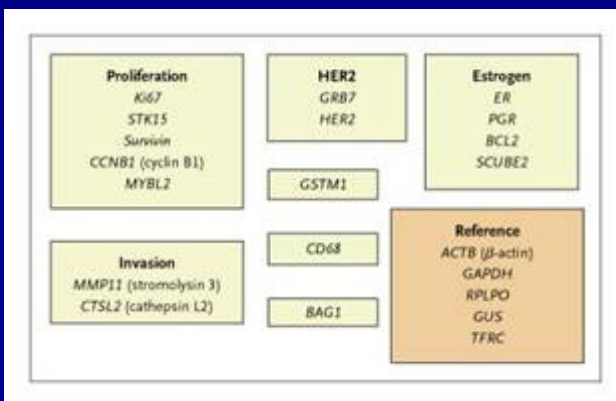
Sotiriou, G. et al. N Engl J Med 2009;360:790-800.



21-gene recurrence score assay (Oncotype DX) and benefit from adjuvant CT: NSABP B-20

Paik S et al. N Engl J Med 2004;351:2817-2826
 Paik S et al. J Clin Oncol 2006; 24:3726-34

- 2363 pts, ER+ N-
- Tam vs TAM + CMF or MF
- 651 pts assessable
- 21-gene assay (Oncotype DX)
- Recurrence score:
 - likelihood of breast cancer recurrence within 10 years
 - from a mathematical function combining the expression values of 16 breast cancer-related genes and five reference genes.

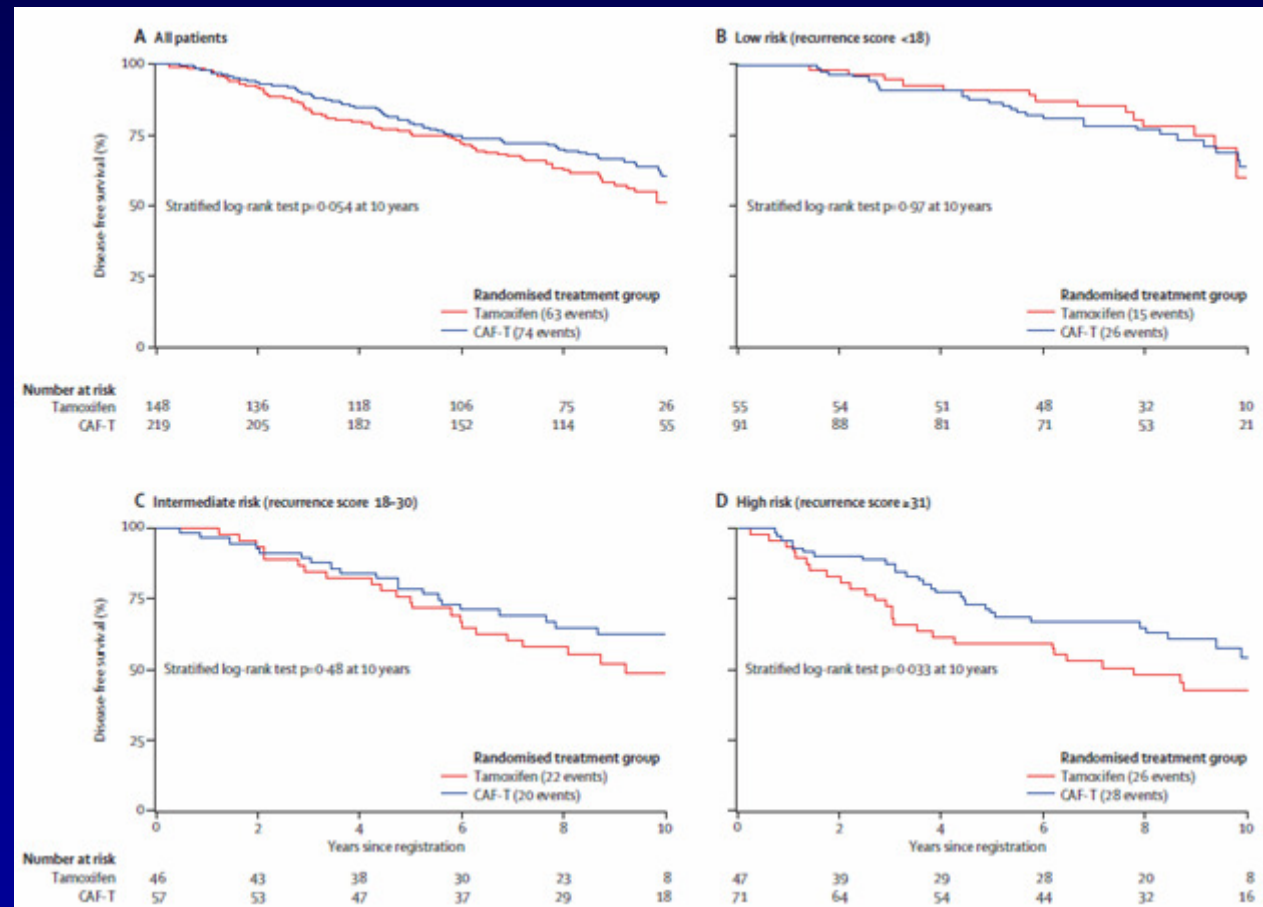


- Test for interaction between chemotherapy treatment and RS statistically significant ($P = .038$)
- Significance maintained in multivariate analysis

21-gene recurrence score assay (Oncotype DX) and benefit from adjuvant CT: SWOG-8814 INT-0100

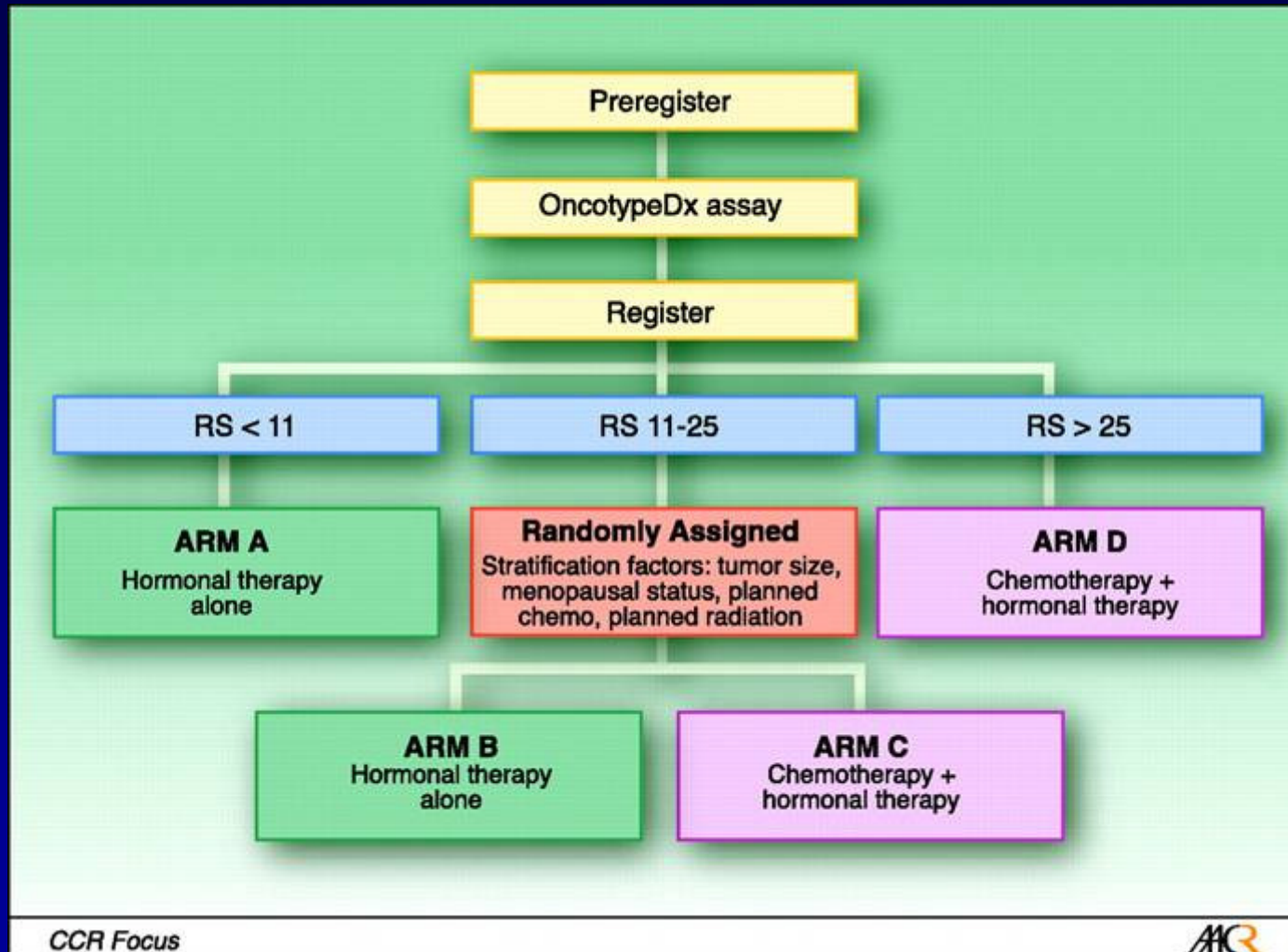
Albain K et al. Lancet Oncol 2009

- 1558 post-menop. pts, ER+ N+
 - Tam
 - CAF x 6 + Tam (CAFT)
 - CAF x 6 → Tam CAF-T
- 367 assessable for RS
- CAF-T vs Tam



- Similar outcomes were seen for overall survival and breast-cancer-specific survival
- RS by treatment interaction significant in the first 5 years for DFS ($p=.029$) and for OS ($p=.016$)
- Interaction remain significant after adjustment for clinical and pathological covariates

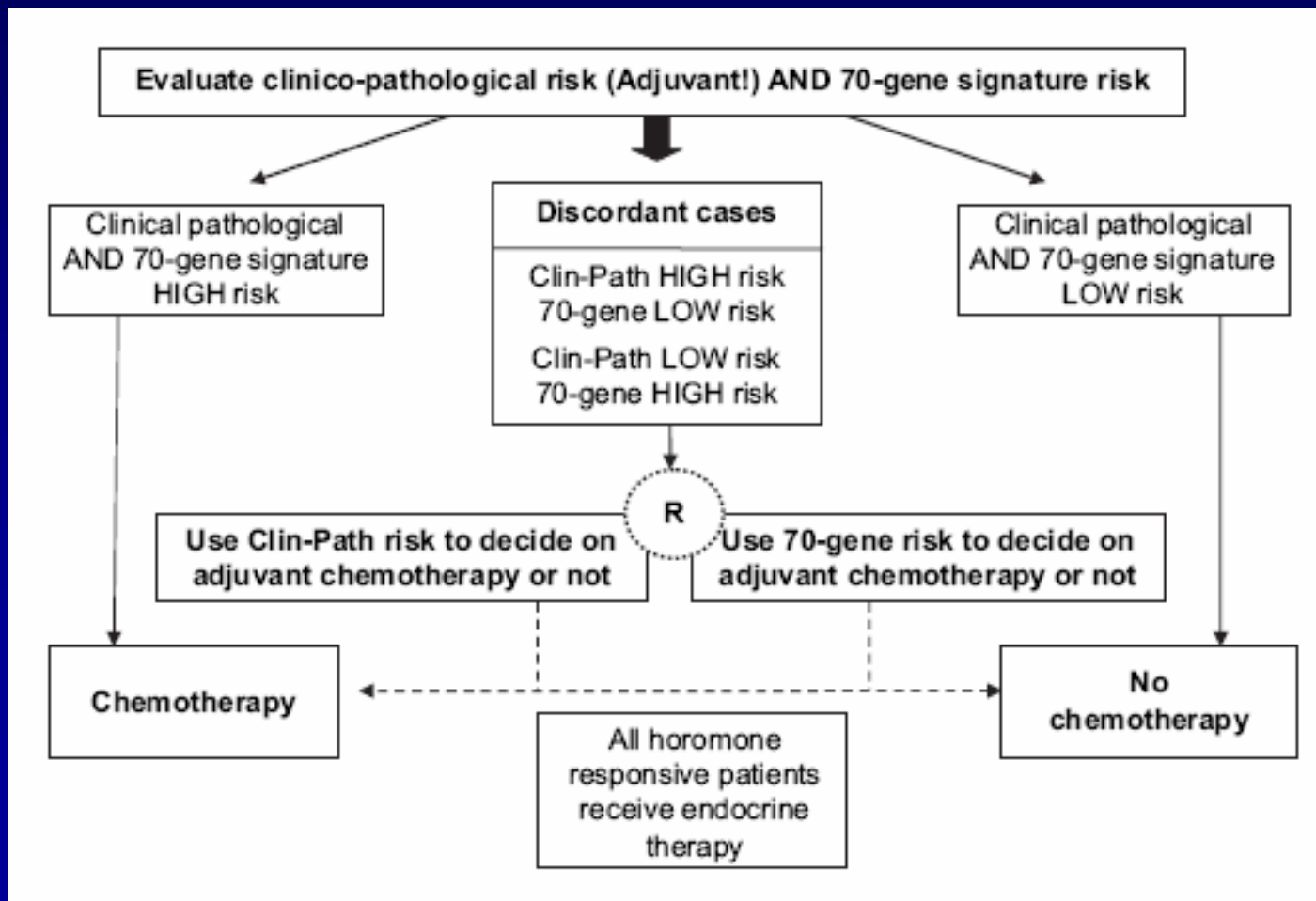
Trial Assigning Individualized Options for Treatment (TAILORx).



Dowsett M , Dunbier A K Clin Cancer Res 2008;14:8019-8026

MINDACT (Microarray In Node-negative Disease may Avoid Chemotherapy Trial)

Which prognostic score (genomic vs clinico-pathological) better identifies N- patients who need adjuvant chemotherapy?



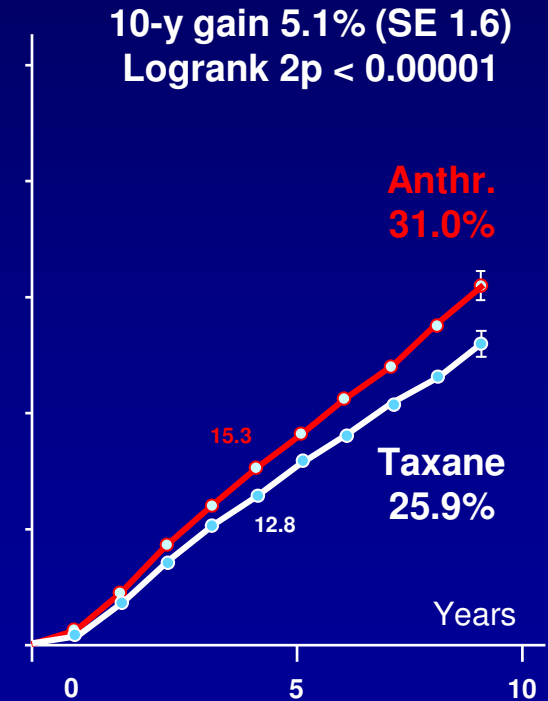
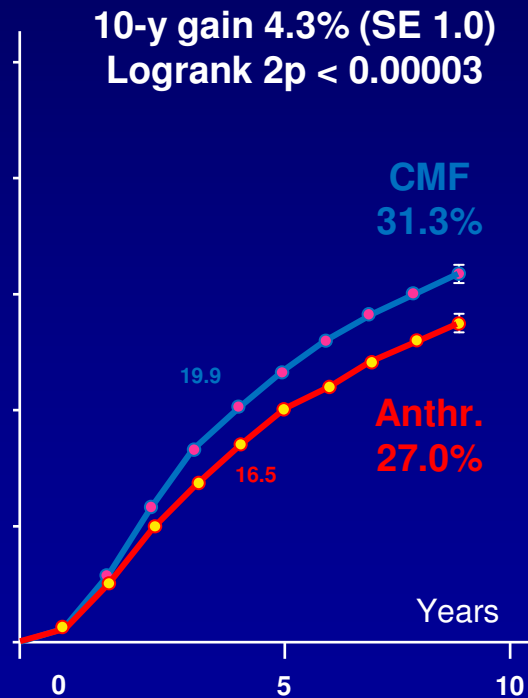
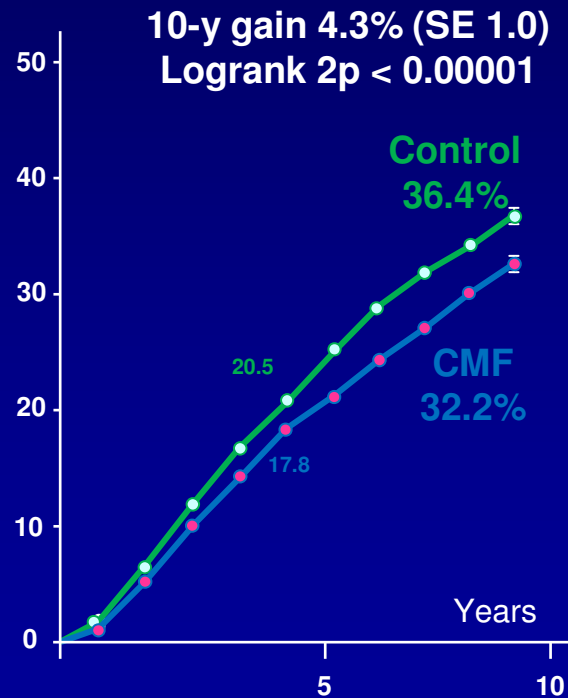
Type of chemotherapy

CT evolution & new agents

EBCTCG Meta-analyses 2005-6

Peto R, et al. SABCS 2007

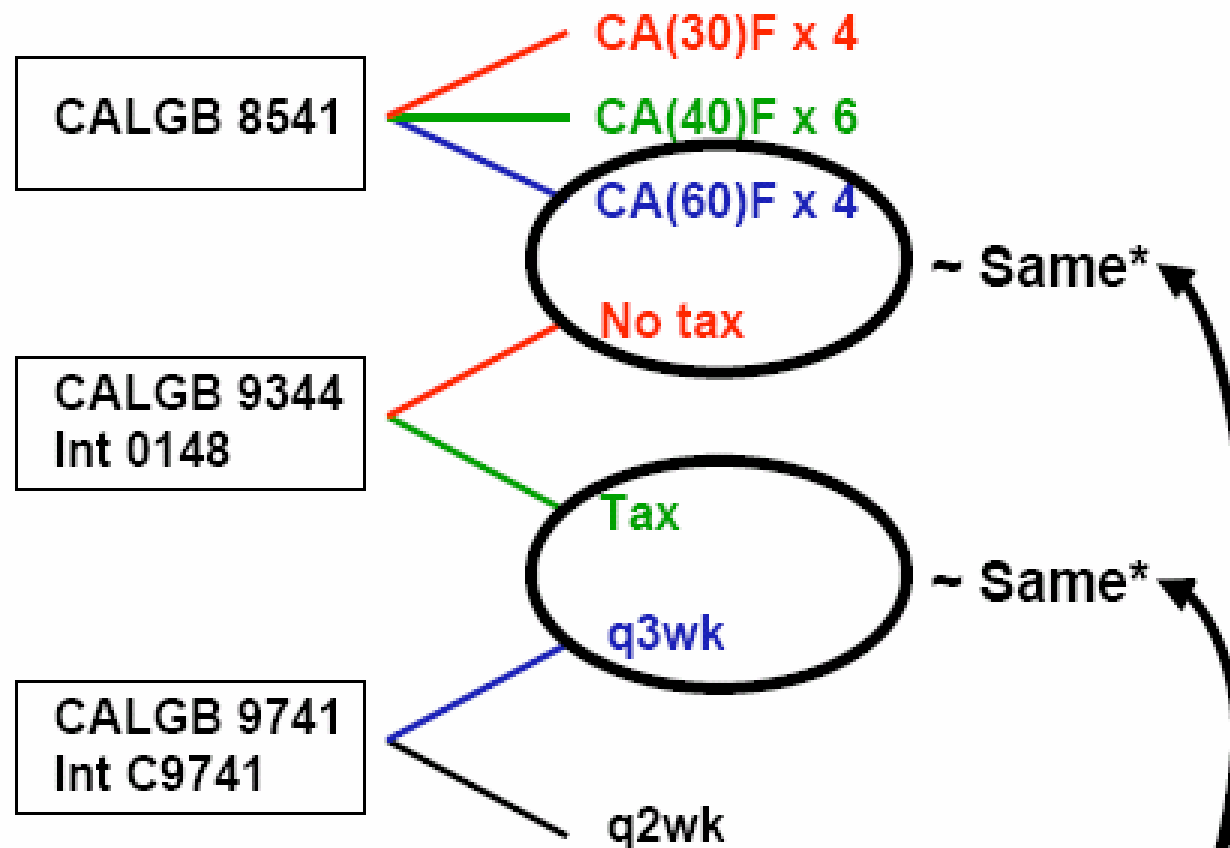
Breast cancer mortality



Taxanes > Antraciline > CMF > No Chemo

CT intensification CALGB / US Intergroup Trials, N+

Berry D et al. JAMA 2006; 295:1658-67



* After adjusting, no significant differences

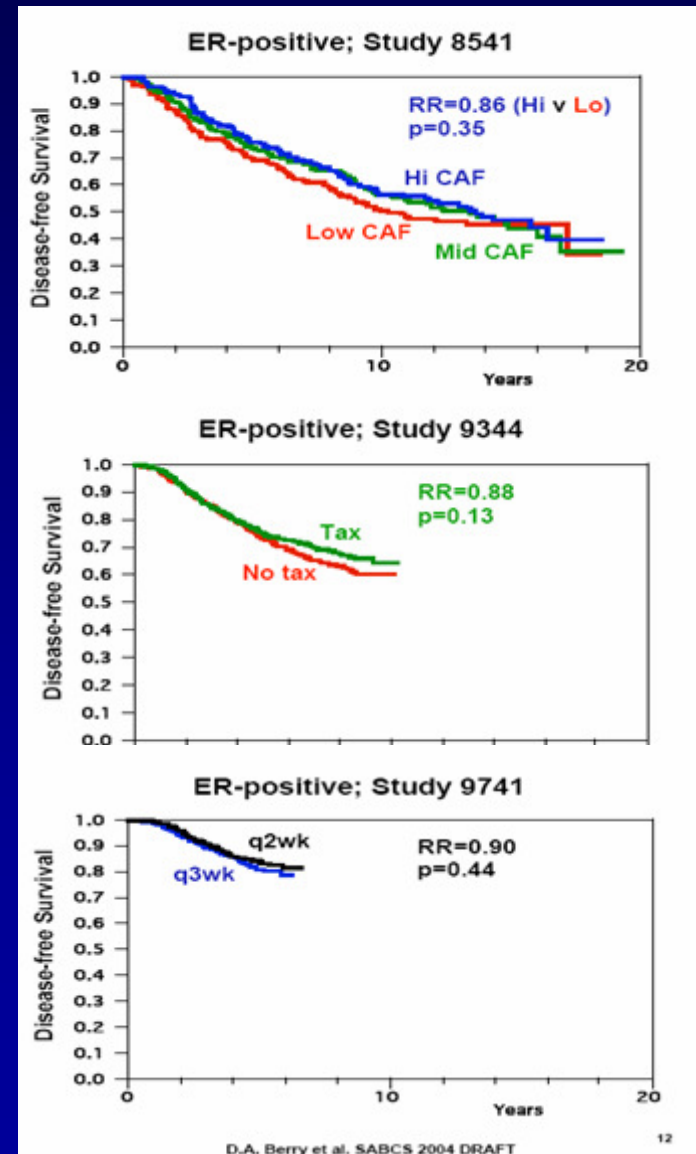
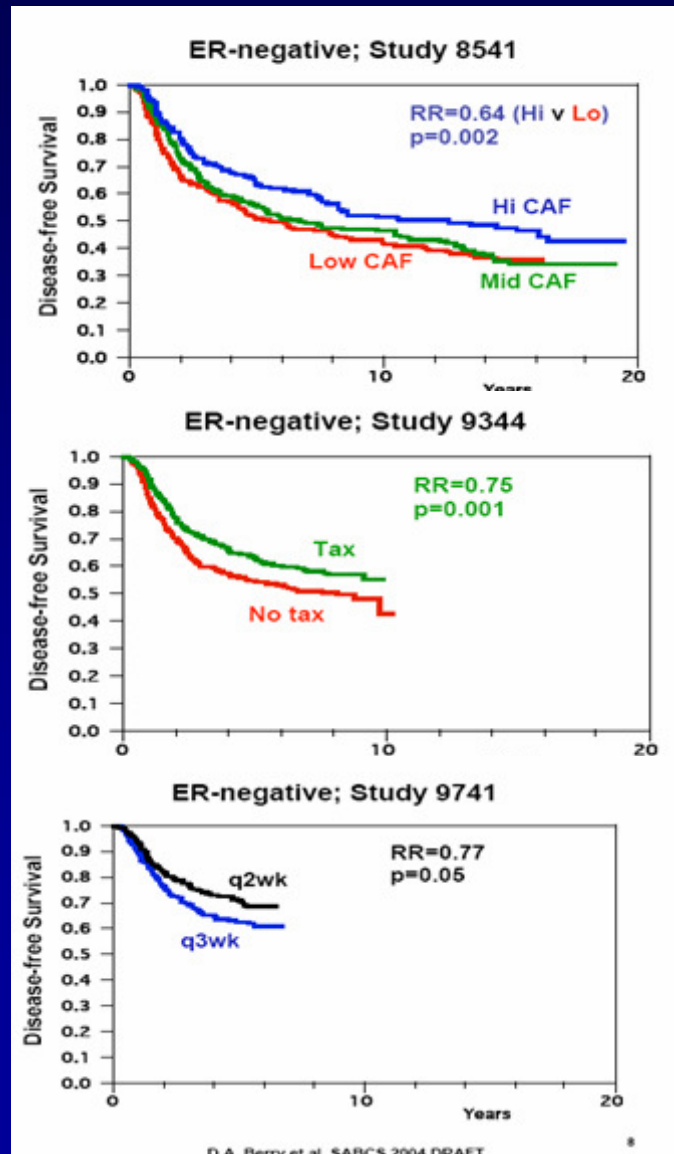
Benefit from CT according to ER expression

CALGB / US Intergroup Trials, N+

Berry D et al. JAMA 2006; 295:1658-67

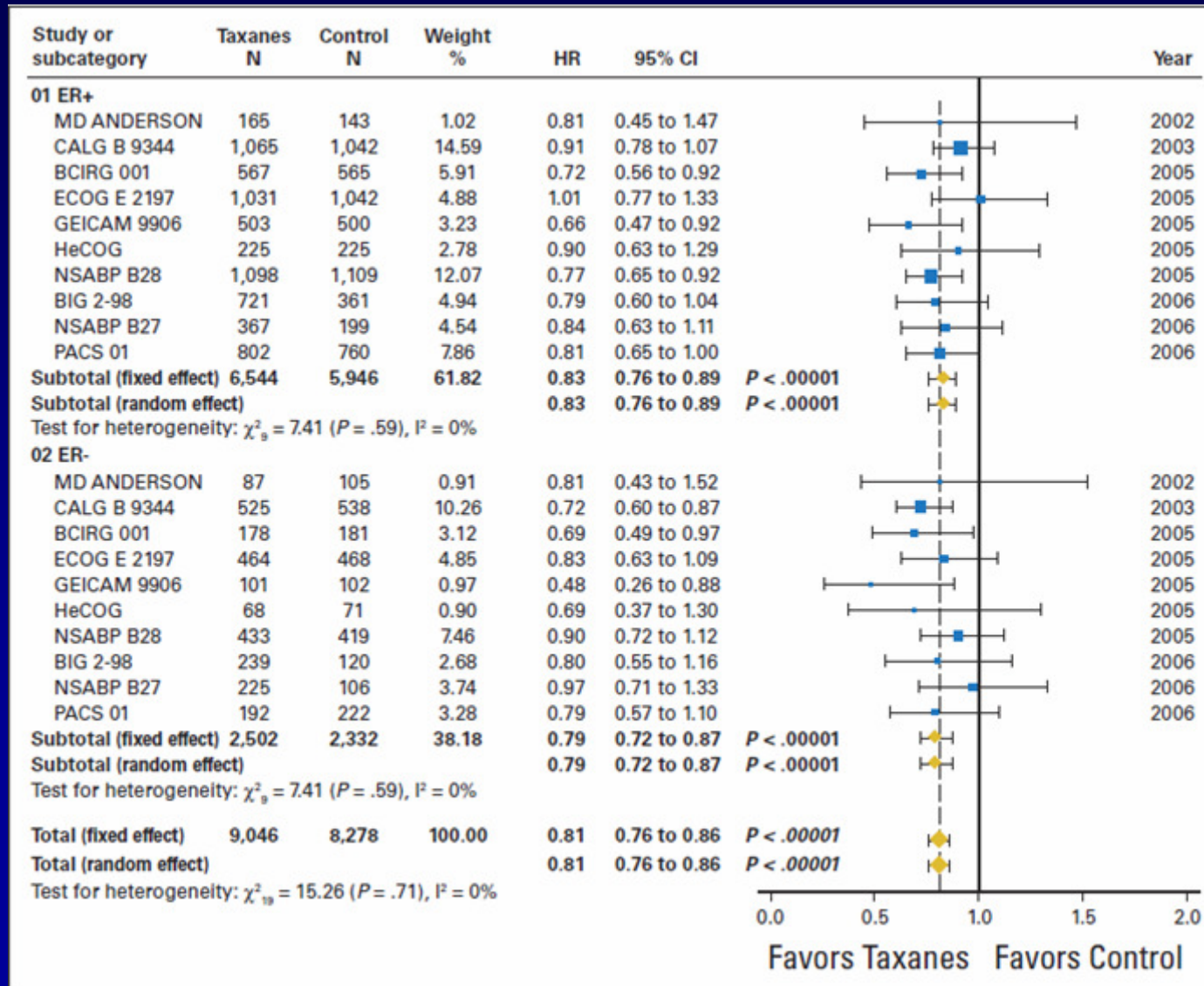
ER-

ER+



Taxane-based vs anthracycline-based adjuvant CT meta-analysis: DFS according to ER status

De Laurentiis, M. et al. J Clin Oncol; 26:44-53 2008



Taxane-based vs anthracycline-based adjuvant CT: Meta-analysis of DFS according to ER & HER2

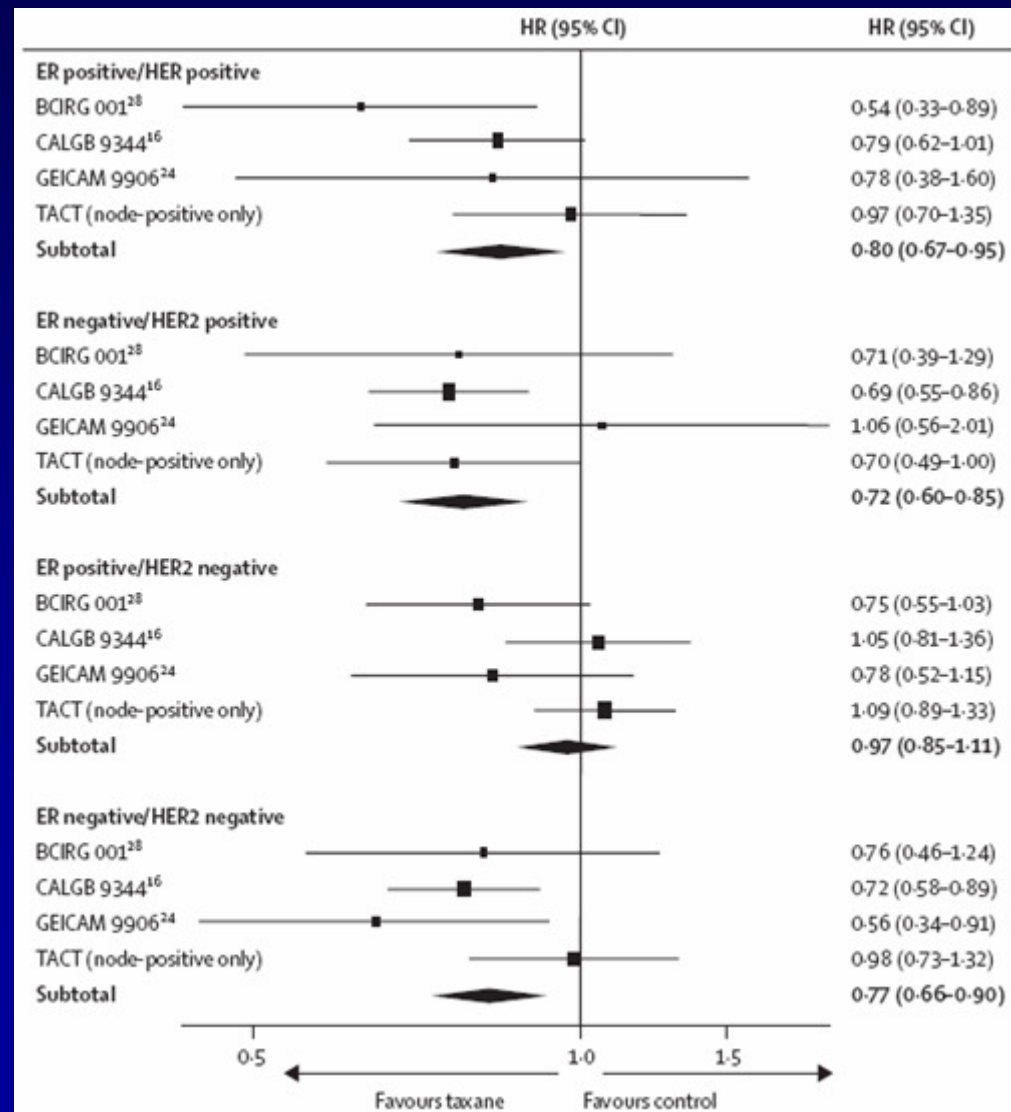
Ellis P et al; Lancet 2009; 373: 1681-92

Luminal B

HER2

Luminal A

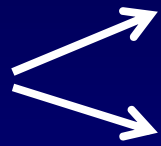
Triple negative



Breast cancer subtypes and response to docetaxel (BCIRG 001)

Hugh J et al; J Clin Oncol 2009; 27:1168-1176

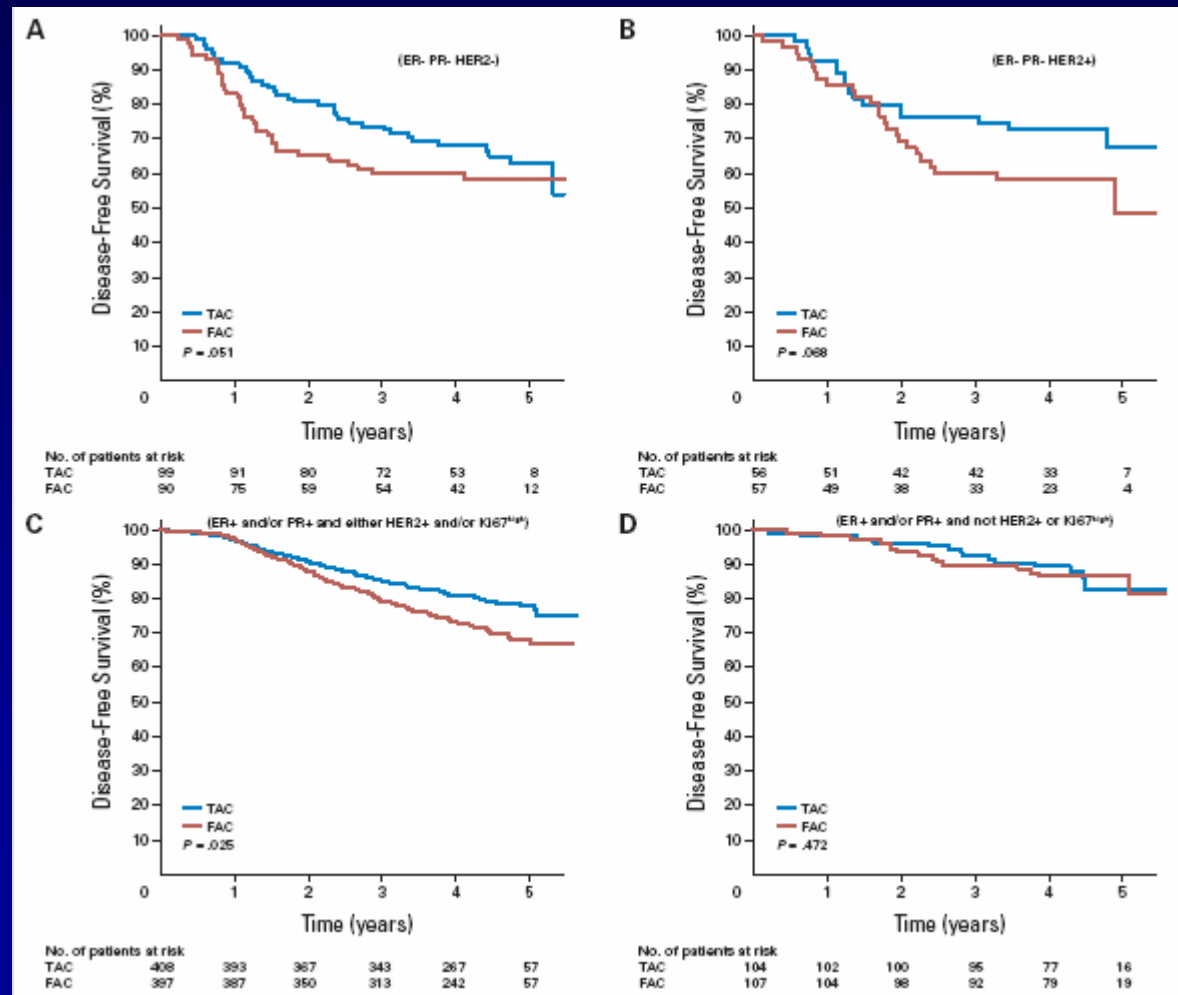
R



FAC x 6

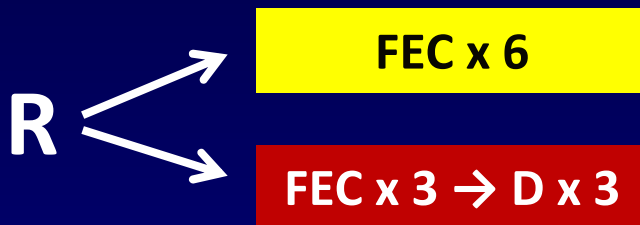
TAC x 6

- 1491 women, N+
- 1,350 patients (91%) had central laboratory assessment
- **luminal A** (ER+ and/or PR+ and not HER2+ or Ki67^{high})
- **luminal B** (ER+ and/or PR+ and HER2+ or Ki67^{high})
- **HER2** (HER2+, ER- and PR-)
- **triple negative** (ER-, PR-, HER2-)

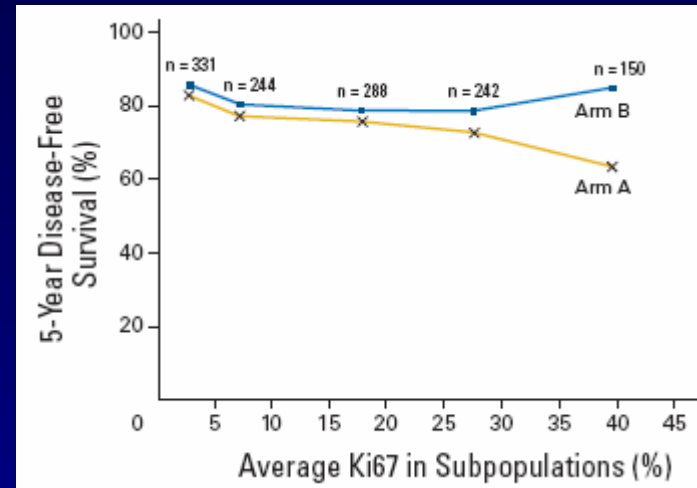


Ki-67 and response to docetaxel in pts with ER+ tumors (PACS01)

Penault-Llorca F et al; J Clin Oncol 2009; 27:2809-15



- 1999 pts N+
- 798 ER+ pts assessable for this substudy



Biomarker	Hazard ratio for relapse associated with docetaxel (95% CI)	Hazard ratio for interaction with docetaxel (95% CI), P
Ki67		
Positive (n = 150)	0.51 (0.26 to 1.01)	0.53 (0.24 to 1.16),
Negative (n = 549)	1.03 (0.69 to 1.55)	.11
HER-2		
Overexpressed (n = 73)	1.34 (0.55 to 3.21)	0.83 (0.35 to 1.94),
Normal (n = 705)	0.85 (0.60 to 1.20)	.66
PR		
Positive (n = 454)	0.83 (0.53 to 1.30)	0.89 (0.47 to 1.66),
Negative (n = 279)	0.86 (0.54 to 1.39)	.71

Predicting response to neoadjuvant ADM + PTX

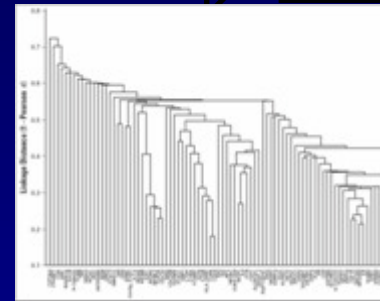
Gianni L et al. J Clin Oncol 2005; 23:7265-77

89 pts
Stage III
breast cancer

RNA from paraffin-
embedded core
biopsies
↓
RT-PCR 384 genes

ADM+PTX x 4

SURGERY:
• 11 pCR (12%)



Univariate analysis

- 86 genes correlated with pCR
- Biological categories:
 - proliferation (MCM6, E2F1, MYBL2)
 - apoptosis (BBC3, BAD, DR4, TP53BP1)
 - invasion and metastasis (FYN and MMP12)
 - Drug resistance-metabolism (ABCC5, ALDH1A1, CYP3A4)

Cluster analysis

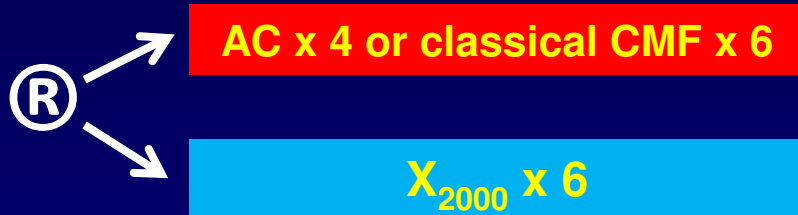
Groups of co-expressed genes:

- *ER* gene cluster (PR, *SCUBE2*, *ER*, *NPD009*, *GATA3*, *IGF1R*, *IRS1*)
 - ↓ likelihood of pCR
- proliferation gene cluster (*CDC20*, *E2F1*, *MYBL2*, *TOP2A*, *FBXO5*, *MCM2*, *MCM6*, *CDC25B*)
 - ↑ likelihood of pCR
- immune-related gene cluster (including *MCP1*, *CD68*, *CTSB*, *CD18*, *ILT-2*, *CD3z*, *FasL*, *HLA.DPB1*, *GBP1*)
 - ↑ likelihood of pCR

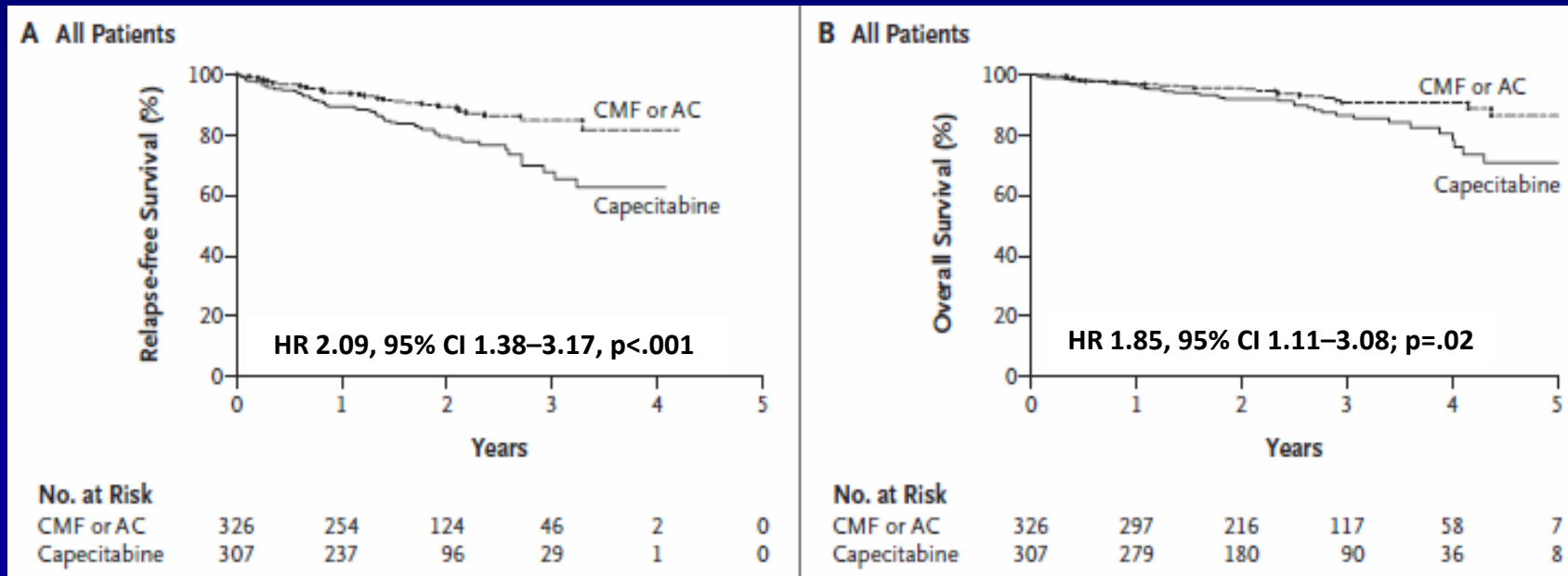
Need for different
chemotherapy regimens?

Adjuvant capecitabine: CALGB 49907

Muss HB, et al. N Engl J Med 2009; 360: 2055-65.



- stage I-III B early breast cancer
- age ≥ 65 y (2/3 ≥ 70 y, 5% ≥ 80 y)
- 633 pts: 133 CMF, 184 AC, 307 capecitabine
- non-inferiority trial, adaptive Bayesian design



The comparisons of capecitabine with AC or CMF were qualitatively the same

Adjuvant capecitabine: CALGB 49907

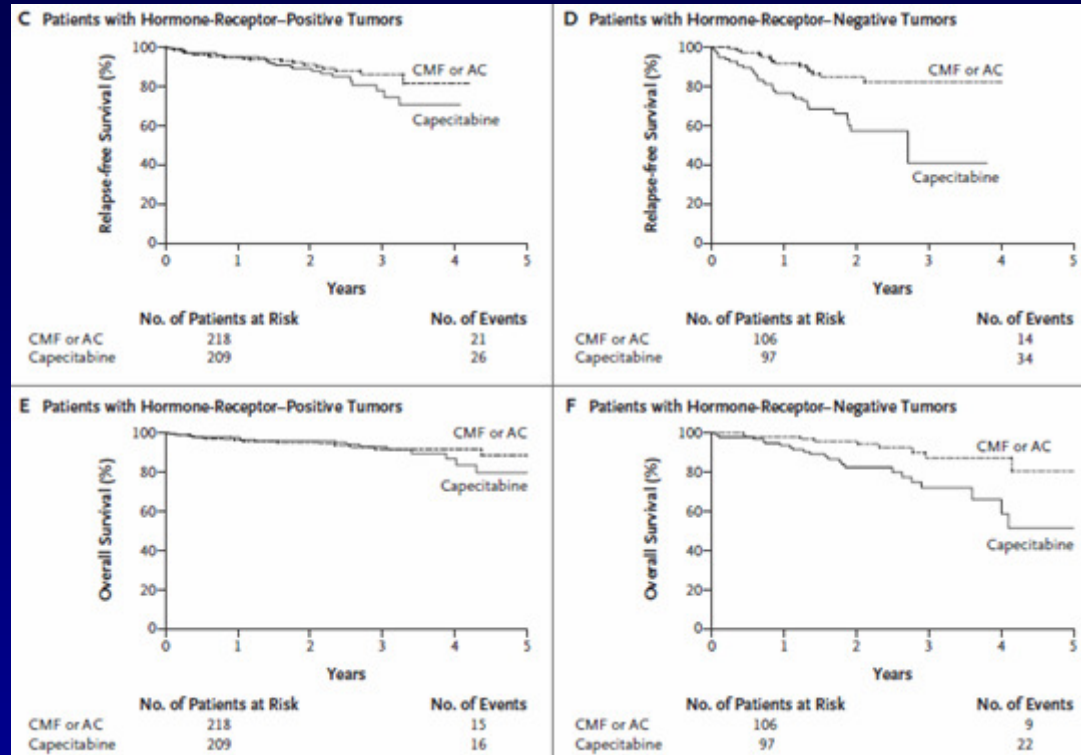
Muss HB, et al. N Engl J Med 2009; 360: 2055-65.

Treatment * hormone-rec. interaction significant for both RFS and OS

Hormone-rec. negative pts receiving cape (vs all others):

RFS HR: 4.39, 95%CI 2.9-6.7, p<.001

OS HR: 3.76, 95%CI 2.23-6.34, p<.001



Adverse Events	CMF n. pts (%)	AC n. pts (%)	Capecitabine n. pts (%)
Death	0	0	2
≥1 G3/4 AE	92 (70)	109 (60)	101 (34)
≥1 G3/4 hemat. AE	68 (52)	99 (54)	7 (2)

St Gallen Consensus 2009

Goldhirsch A, et al. Ann Oncol 2009

Chemoendocrine therapy in patients with ER-positive, HER2-negative disease

	Relative indications for chemoendocrine therapy	Factors not useful for decision	Relative indications for endocrine therapy alone
ER and PgR	Lower ER and PgR level		Higher ER and PgR level (≥50% tumor cells)
Histological grade	Grade 3	Grade 2	Grade 1
Proliferation	High ^a	Intermediate ^a	Low ^a
Nodes	Node positive (≥4)	Node positive (1-3)	Node negative
PVI	Extensive PVI		Absence of extensive PVI
pT size	>5 cm	2.1–5 cm	2 cm
Patient preference	Use all available treatments		Avoid CT-related side-effects
Gene signature ^b	High score	Intermediate score	Low score

- a) Ki67-labelling index (e.g. low <15%; intermediate 16%–30%; high >30%); frequency of mitoses; genetic signatures including proliferative genes.
- b) if readily available, could assist in deciding whether to add chemotherapy in cases where its use was uncertain after consideration of conventional markers.
- If many intermediate criteria are present, they tip the balance toward the use of CT
 - pT1a pN0 ER+ should be offered ET alone even in presence of features indicating CT

Conclusions

- **The degree of benefit from chemotherapy is not the same across risk categories, but differs in different tumor subtypes, even within hormone receptor-positive tumors.**
- **ER and PgR levels, Ki-67, HER2 expression, grade, and consideration of recurrence risk, may assist in selection of pts**
- **Multigene assays may be helpful particularly when classical pathological features are not useful for decision**
- **Discussion with the patient and consideration of patient's preference pivotal for decision**