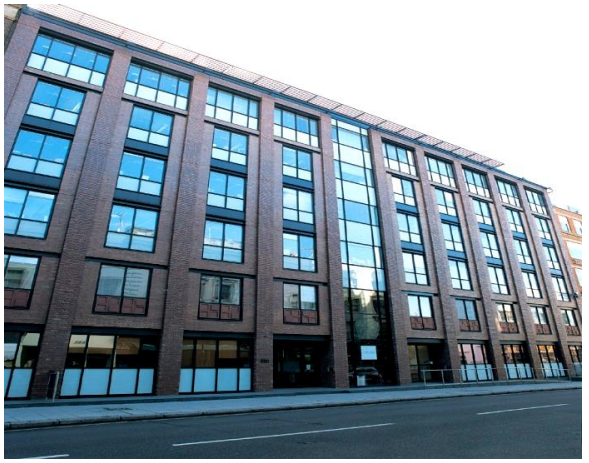
Late Recurrence in ER+ve Breast Cancer: Risk Prediction and Treatment



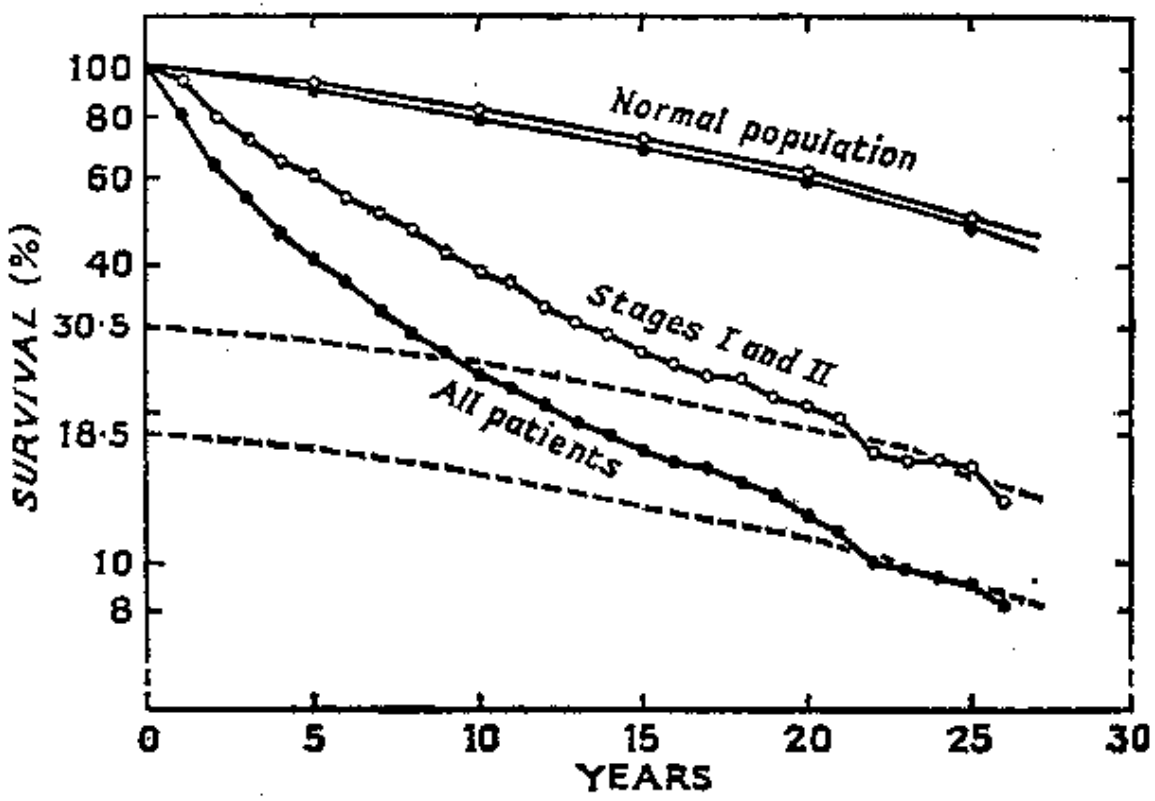
Ian E Smith

Royal Marsden Hospital and Institute of Cancer Research, London

April 2019, Korea

The Curability of Breast Cancer

DIANA BRINKLEY * J. L. HAYBITTLE
Addenbrooke's Hospital, Cambridge



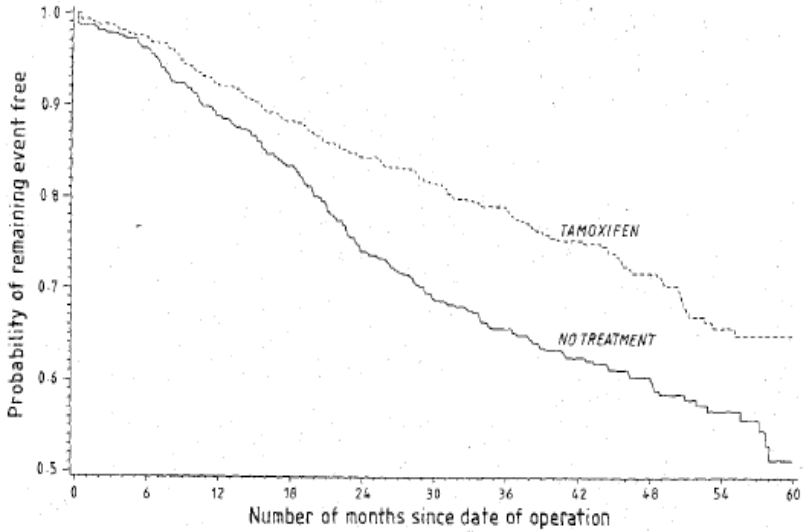
Survival-rates after treatment in 704 cases of breast cancer compared with expected survival of normal populations of same age distribution.

Lancet July 19th 1975

CONTROLLED TRIAL OF TAMOXIFEN AS SINGLE ADJUVANT AGENT IN MANAGEMENT OF EARLY BREAST CANCER

Analysis at Six Years by Nolvadex Adjuvant Trial Organisation*

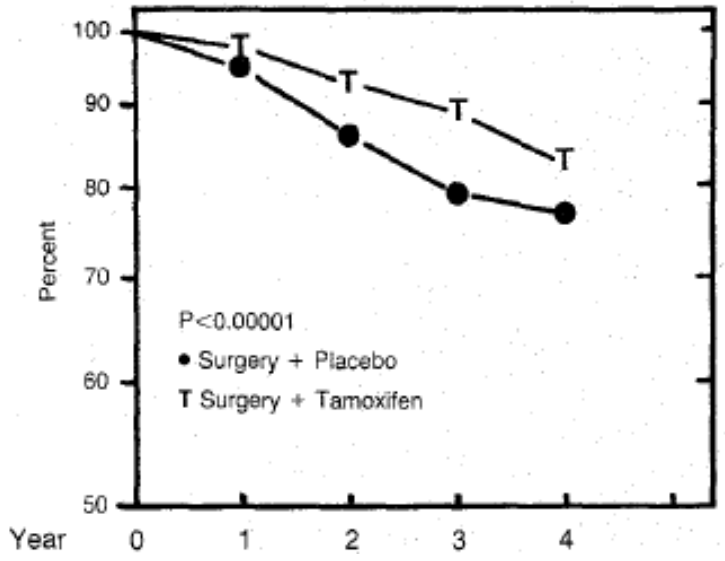
NATO
2 years tamoxifen



Baum et al (NATO Trialists) Lancet 1985

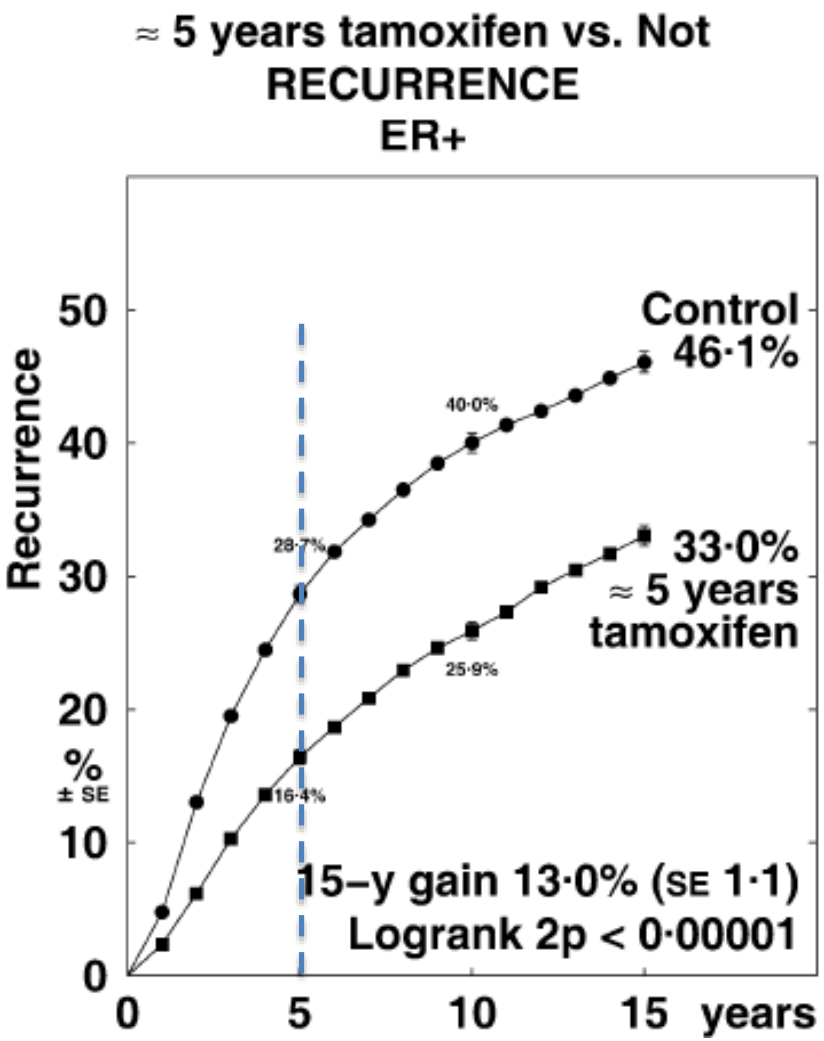
A RANDOMIZED CLINICAL TRIAL EVALUATING TAMOXIFEN IN THE TREATMENT OF PATIENTS WITH NODE-NEGATIVE BREAST CANCER WHO HAVE ESTROGEN-RECEPTOR–POSITIVE TUMORS

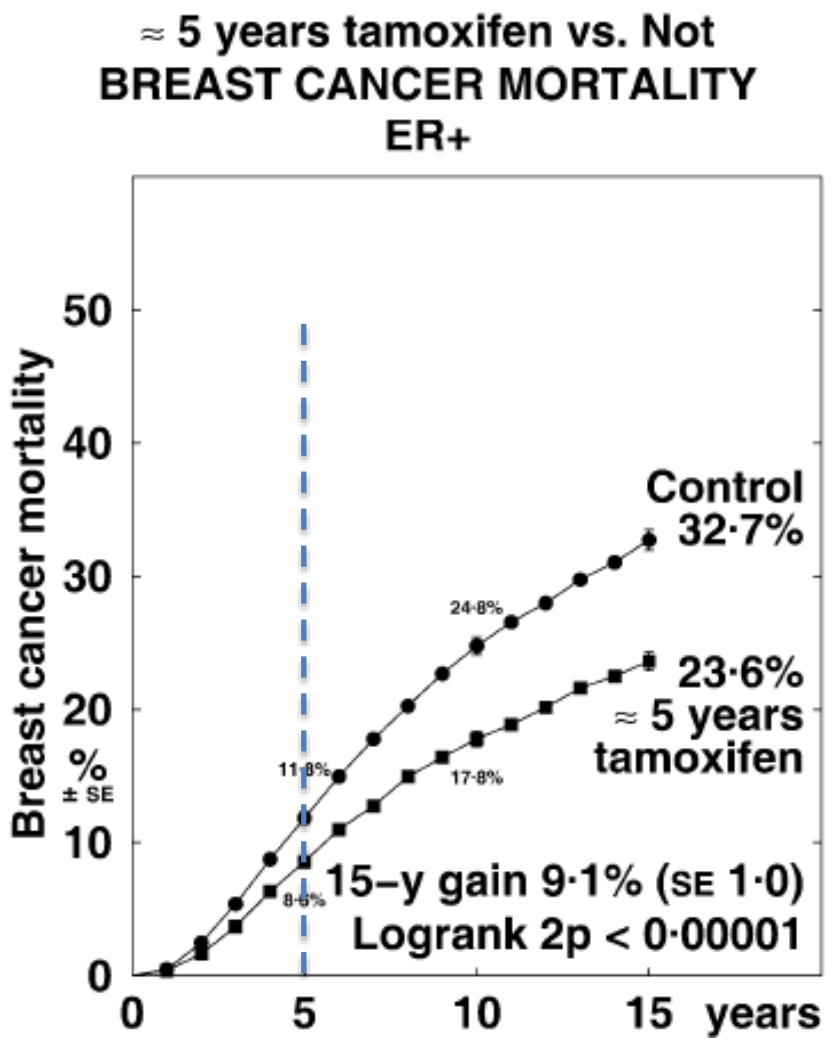
NSABP-B14
5 years tamoxifen



Fisher et al NEJM 1989 320: 479

Adjuvant Tamoxifen

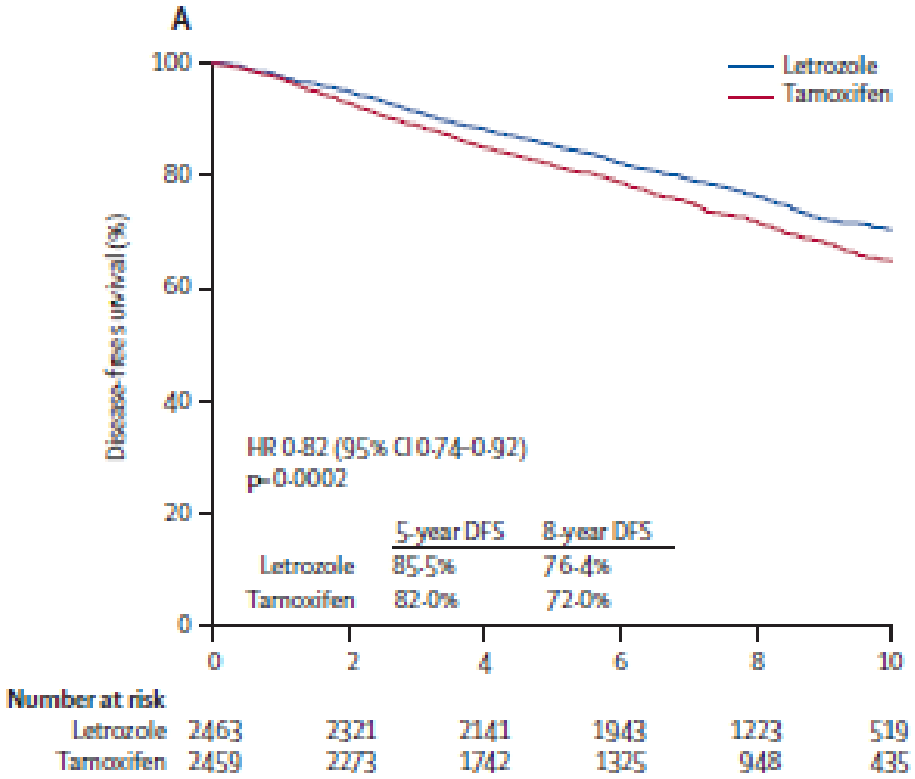




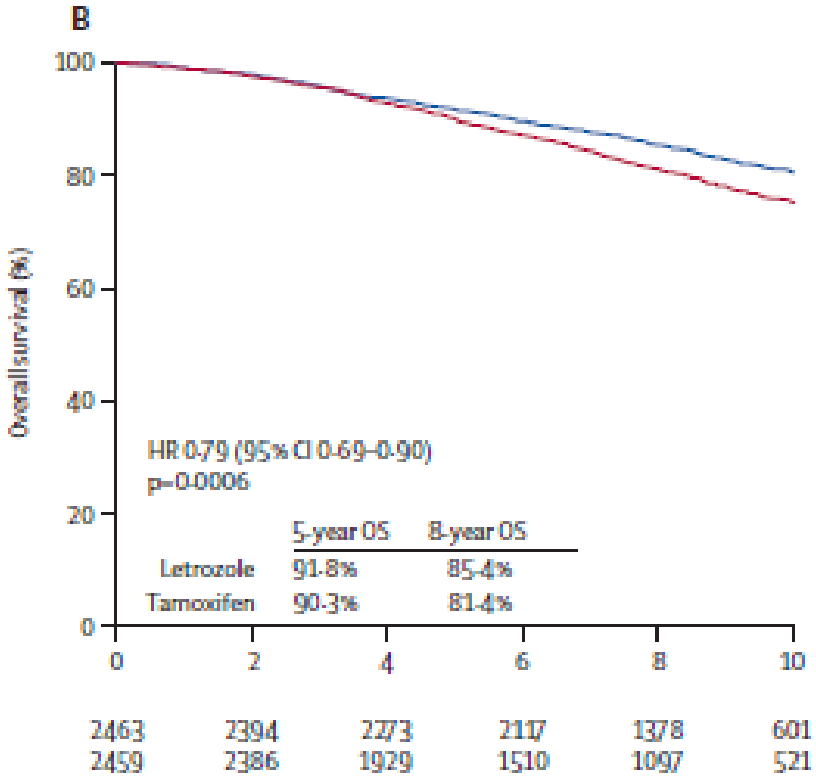
Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet. 2011;378(9793):771-84.

Adjuvant Letrozole v Tamoxifen: BIG 1-98 Median 8 Years FU

DFS



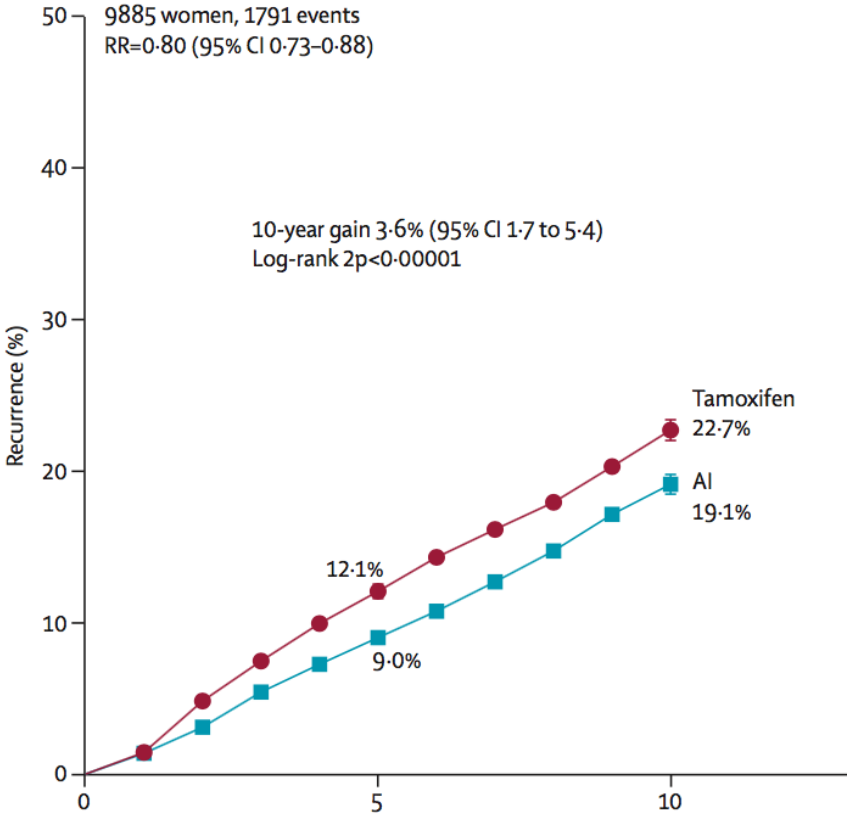
OS



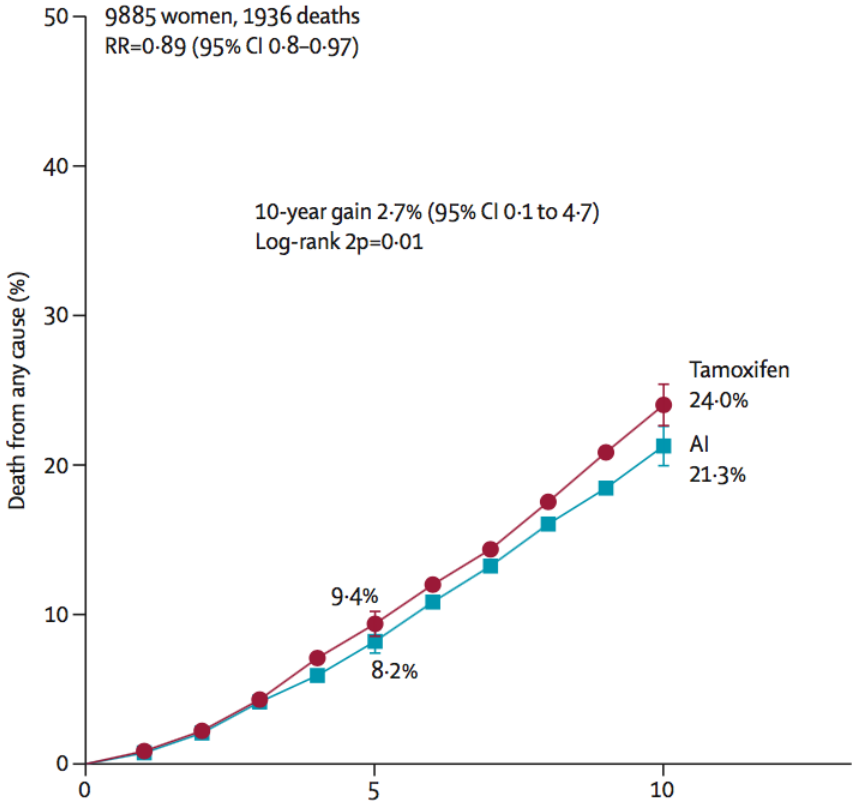
Regan et al Lancet Oncology 12:1101 2011

Aromatase Inhibitors v Tamoxifen in Early Breast Cancer: Meta-analysis

Recurrence



Deaths



EBCTCG Lancet 2015

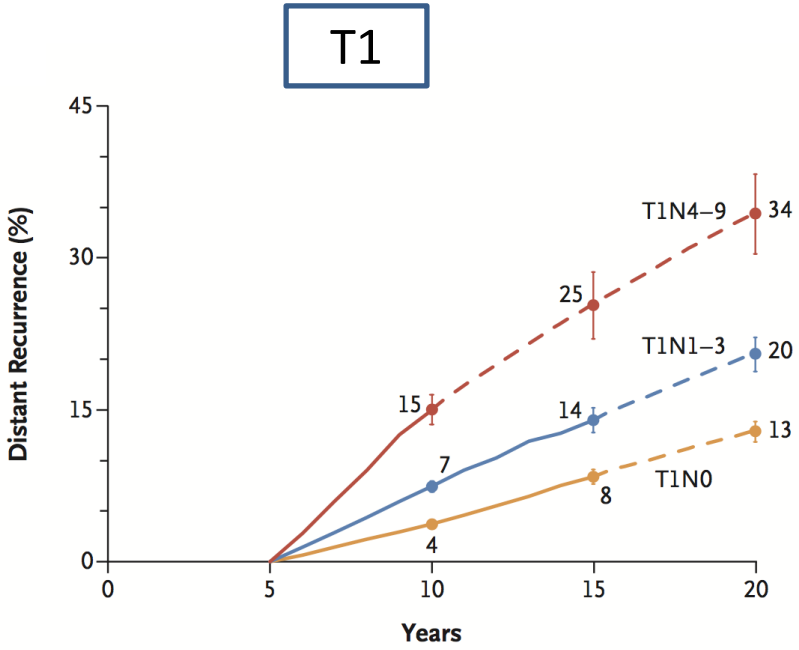
So Even After 5 years of Endocrine Therapy, Which Patients Are Still At Risk of Late Recurrence?

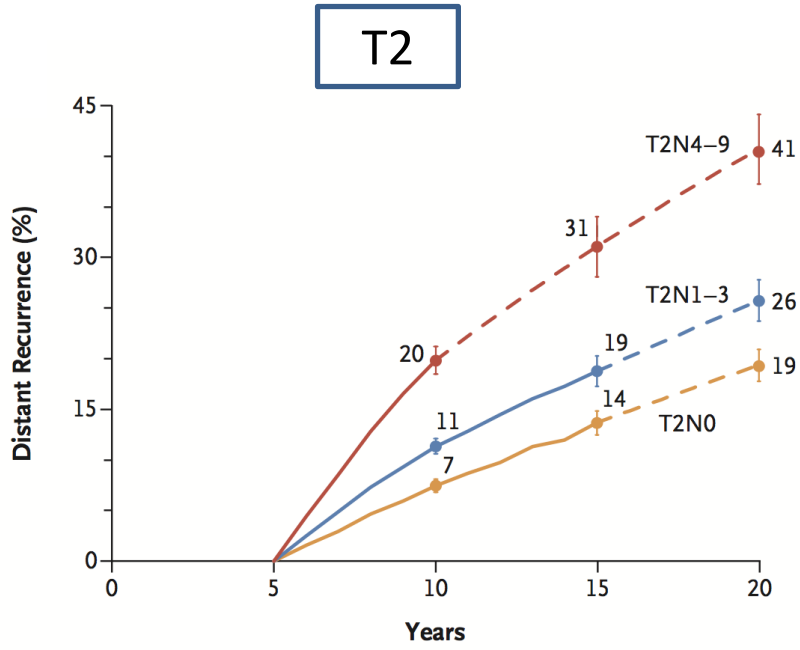
Late Distant Recurrence and Mortality in Women with ER+ve Breast Ca Assigned to Stop Endocrine Therapy at 5 Yrs

- EBCTG Oxford
- 63,000 patients
- 88 Trials

Pan et al. NEJM 2017;377:1836-46

Distant Recurrence by Nodal Status & T Size
Patients Without Recurrence at 5 Yrs
Years 5-20



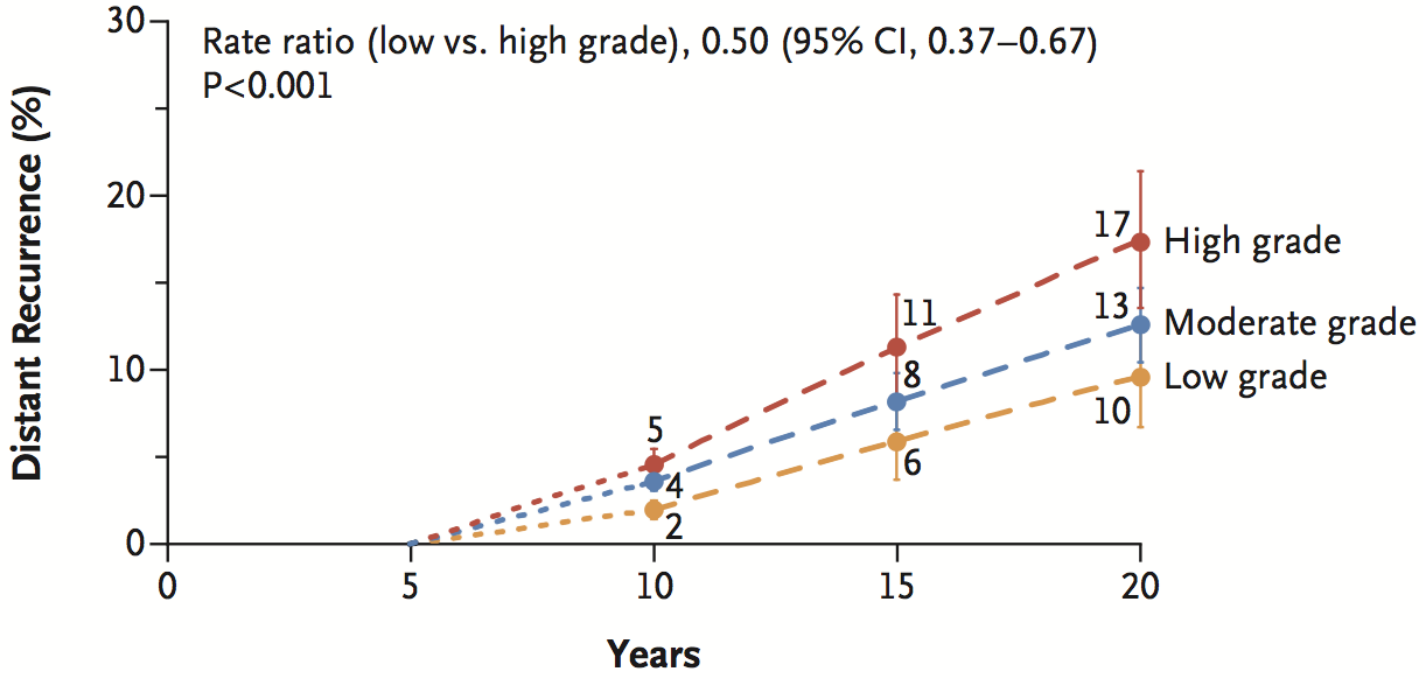


No. at Risk				
T1N4–9	3,832	1193	214	32
T1N1–3	14,342	5138	817	154
T1N0	19,402	8020	2345	440

No. at Risk				
T2N4–9	4,952	1517	285	51
T2N1–3	10,950	3551	614	114
T2N0	9,445	3901	1129	218

Pan et al NEJM 2017;377:1836-46.

Distant Recurrence by Grade in T1 Tumours Patients Without Recurrence at 5 Yrs 5-20yrs



No. at Risk				
High grade	3054	1010	188	2
Moderate grade	7363	2761	474	6
Low grade	3524	1258	239	6

Pan et al NEJM N Engl J Med 2017;377:1836-46.

Risk of Late Recurrence Relates to NODES, SIZE, GRADE

Variable	Women Who Were Event-free at 5 Yr		Annual Rate of Distant Recurrence		Cumulative Risk from 5 Yr to 20 Yr
	Total	Chemotherapy Scheduled	5 to <10 Yr	10 to 20 Yr	
	no.	*no. (%)*	*percent*		*percent*
Nodal involvement					
N0	28,847	9,136 (32)	1.0	1.1	15
N1–3	25,292	17,280 (68)	1.9	1.7	23
N4–9	8,784	6,664 (76)	3.9	2.8	38
Tumor diameter in N0 only					
T1a or T1b: ≤1.0 cm	5,527	910 (16)	0.5	0.8	10
T1c: 1.1–2.0 cm	13,875	4,034 (29)	0.8	1.1	14
T2: 2.1–3.0 cm	6,700	2,859 (43)	1.5	1.4	19
T2: 3.1–5.0 cm	2,745	1,333 (49)	1.7	1.4	20
Tumor grade in T1N0 only					
Low	3,524	401 (11)	0.4	0.8	10
Moderate	7,363	1,861 (25)	0.7	1.0	13
High	3,054	1,414 (46)	0.9	1.5	17

Nodes

Size

Grade

Genomic Platforms to Predict for **Late** Recurrence?

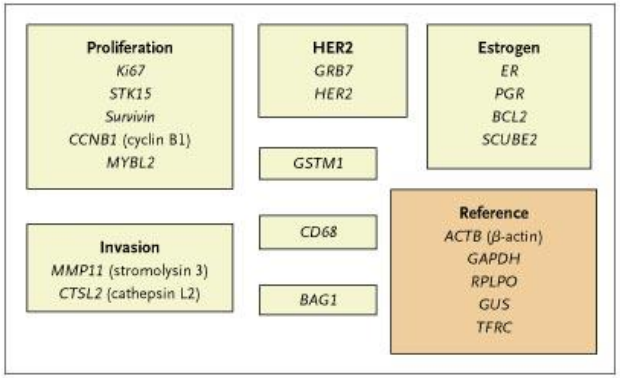
Oncotype DX

Prosigna

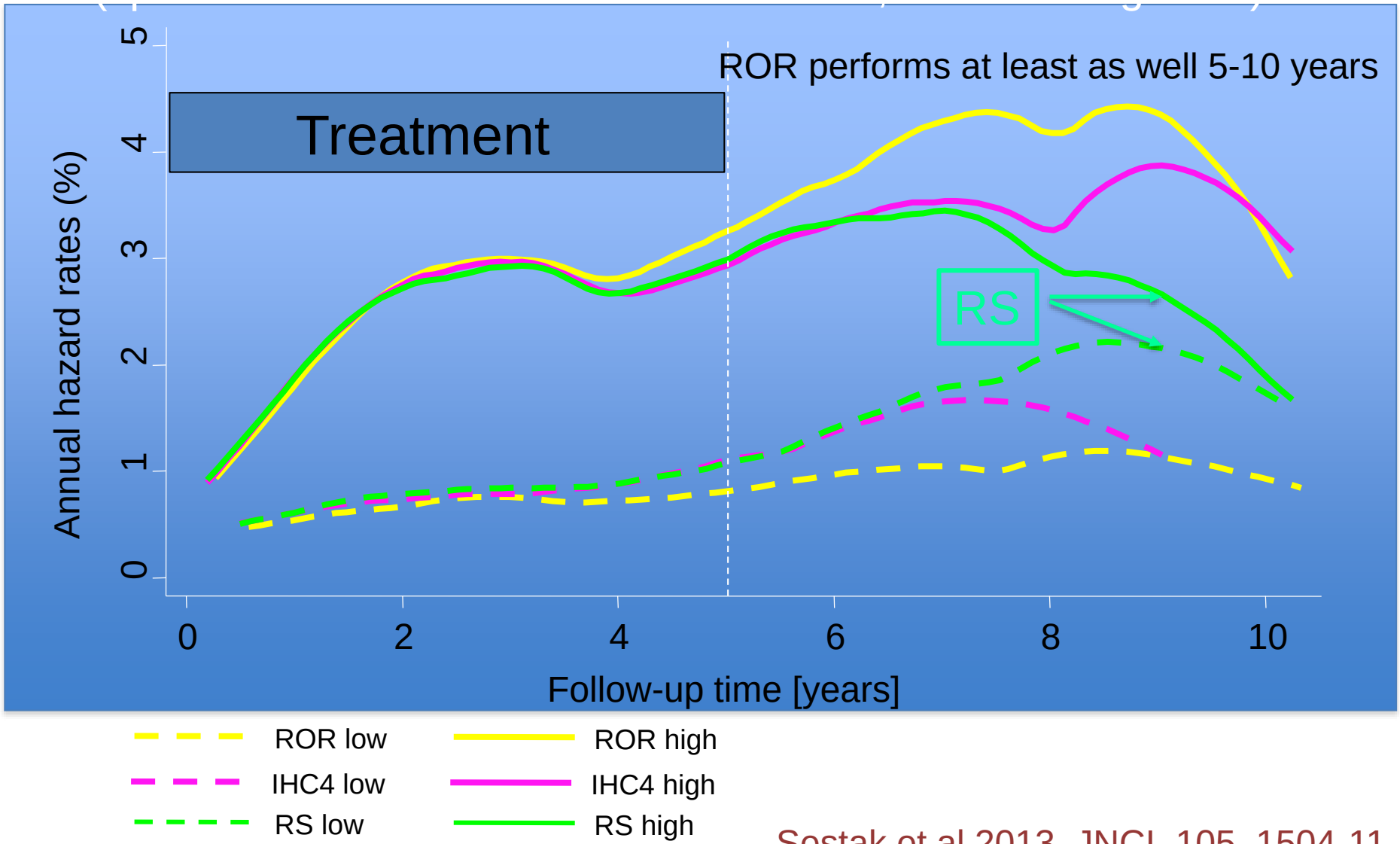
EndoPredict

(IHC4)

Mammoprint

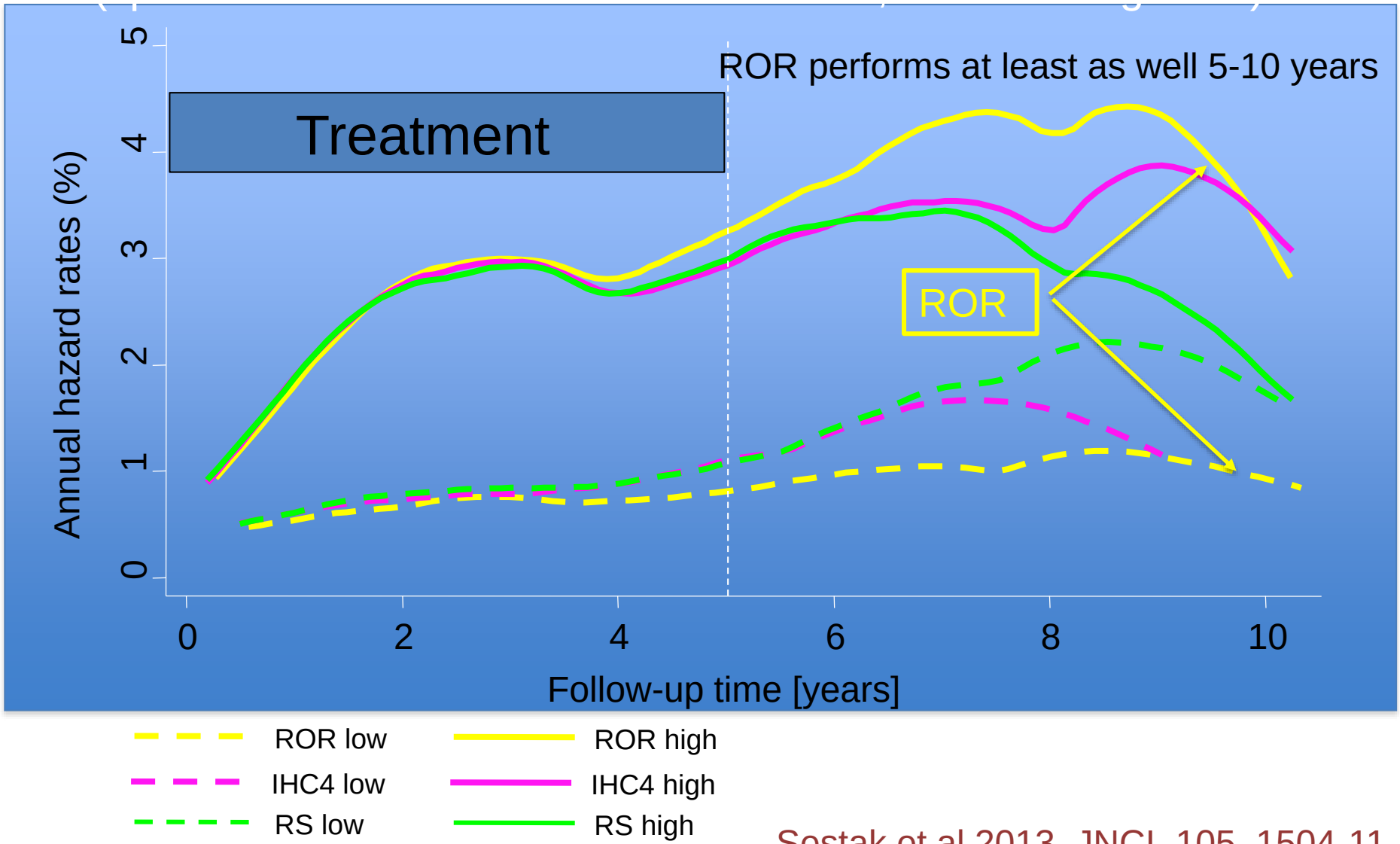


Genomic Platforms? Smoothed hazard rates for RS, IHC4 and ROR in TransATAC over 10 years



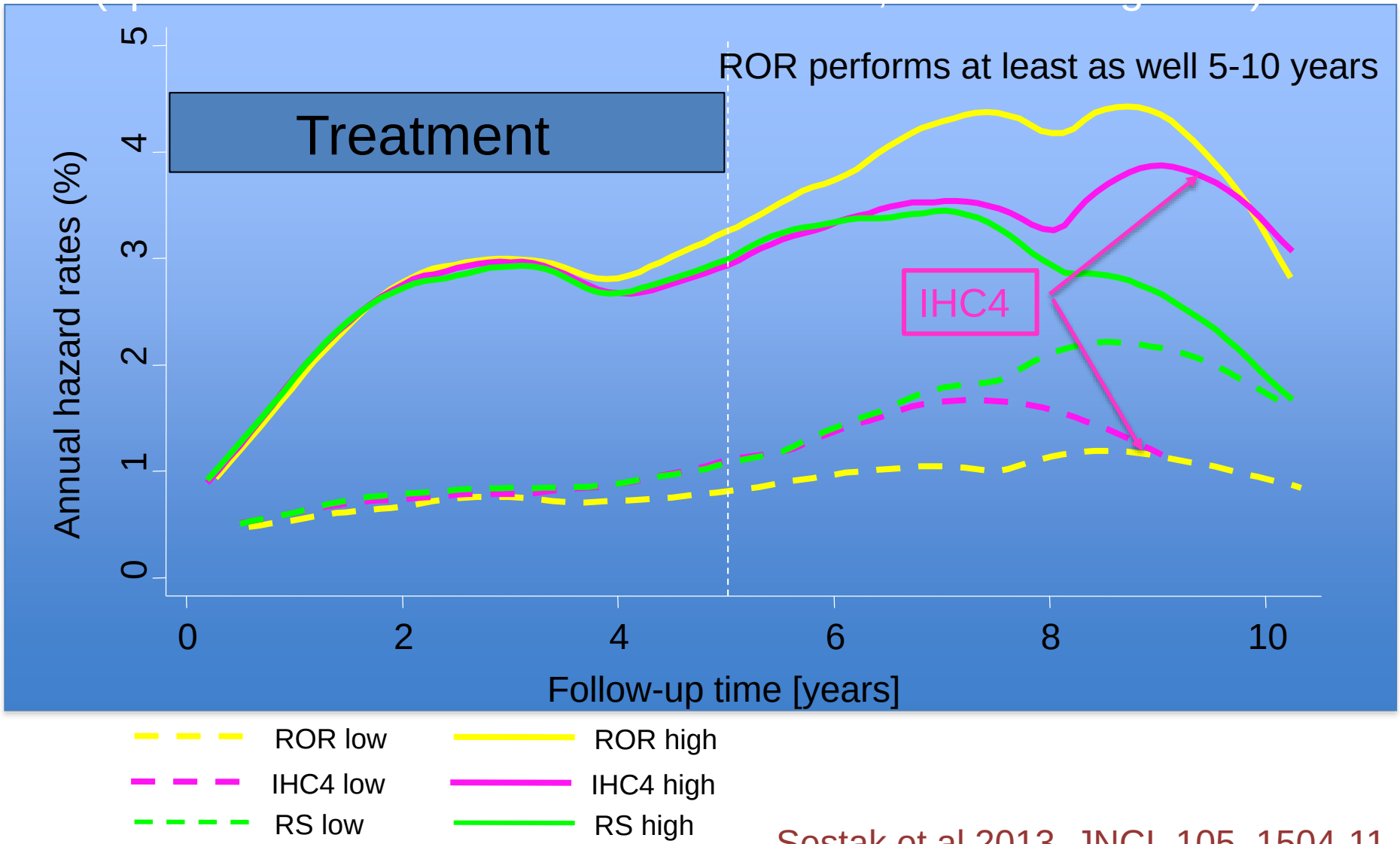
Sestak et al 2013, JNCI, 105, 1504-11

Genomic Platforms? Smoothed hazard rates for RS, IHC4 and ROR in TransATAC over 10 years



Sestak et al 2013, JNCI, 105, 1504-11

Genomic Platforms? Smoothed hazard rates for RS, IHC4 and ROR in TransATAC over 10 years



Sestak et al 2013, JNCI, 105, 1504-11

Direct Comparison of Tests in TransATAC Node Negative:

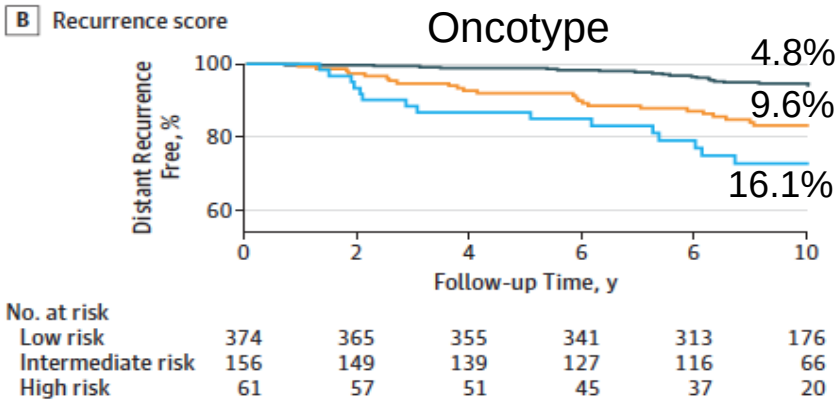
risk years 0-10

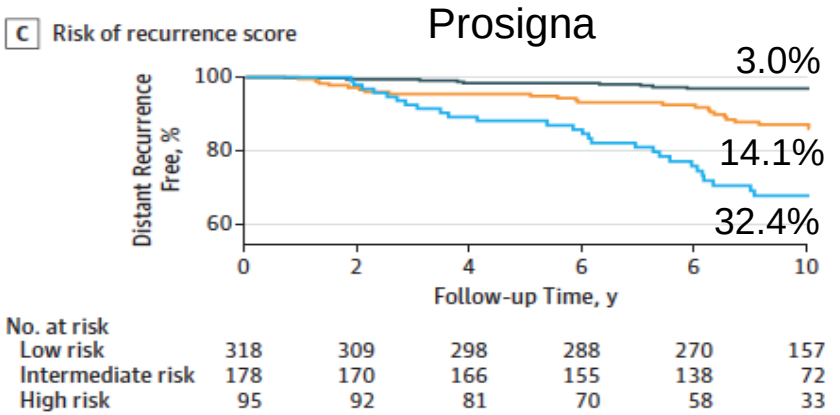
Sestak et al, JAMA Oncol, 2018, 4, 545-553

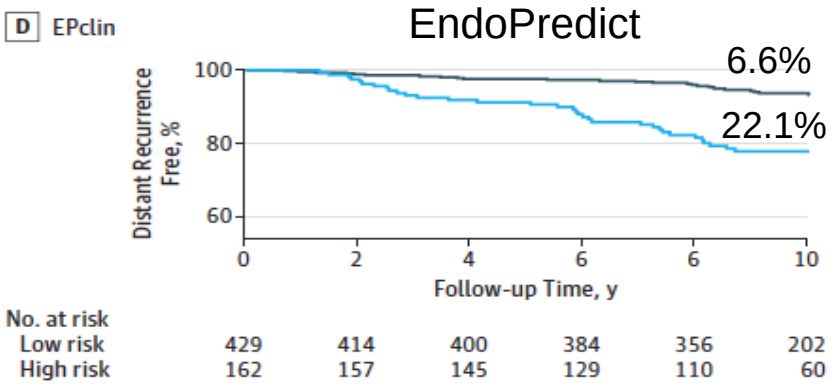
Continuous risk

Gene Signature	Patient Group: Node-Negative Disease (n = 591)	
	HR (95% CI)[a]	C Index (95% CI)
RS	1.69 (1.40-2.03)	0.667 (0.585-0.750)
ROR	2.56 (1.96-3.35)	0.764 (0.707-0.821)
EPclin	2.14 (1.71-2.68)	0.765 (0.716-0.814)

Test-specified categories







Direct Comparison of Tests in TransATAC Node Negative:

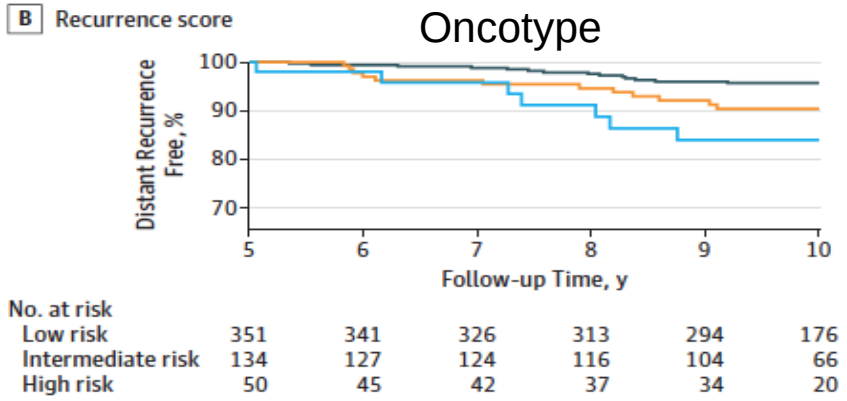
risk years 5-10

Sestak et al, JAMA Oncol, 2018, 4, 545-553

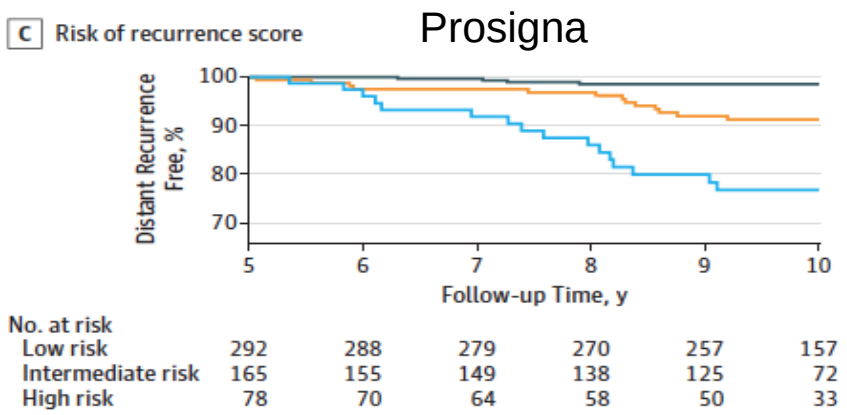
Gene Signature	Patient Group: Node-Negative Disease (n = 535)	
	HR (95% CI)[a]	C Index (95% CI)
RS	1.46 (1.09-1.96)	0.585 (0.467-0.702)
ROR	2.77 (1.93-3.96)	0.789 (0.724-0.854)
EPclin	2.19 (1.62-2.97)	0.768 (0.701-0.835)

Test-specified

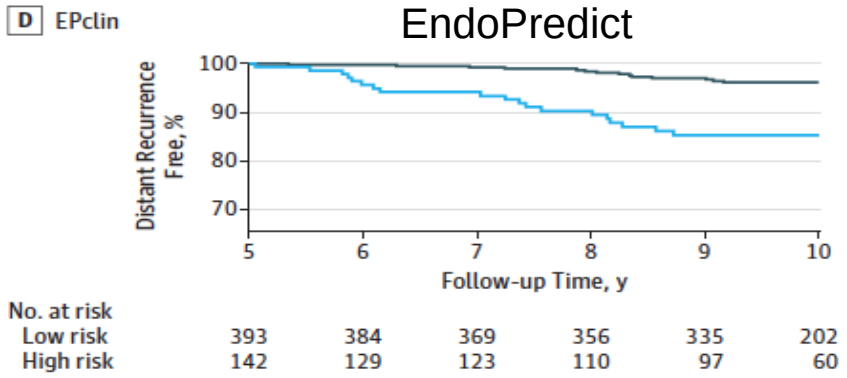
Oncotype



Prosigna



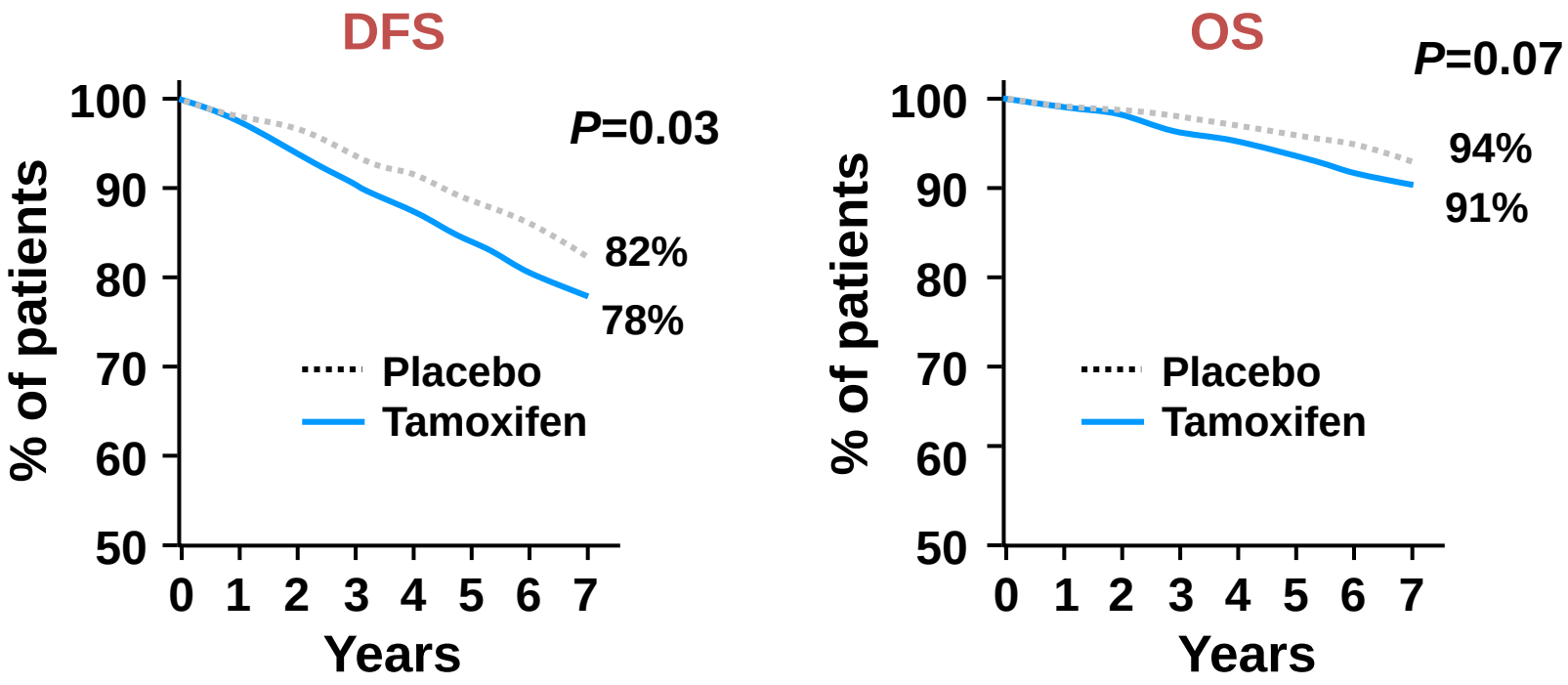
EndoPredict



Would Extended Adjuvant Endocrine Therapy Be Effective In Reducing Late Relapse?

NSABP B-14: After % yrs Tamoxifen , 5 More Years v Placebo

1152 ER+ve N- patients randomised

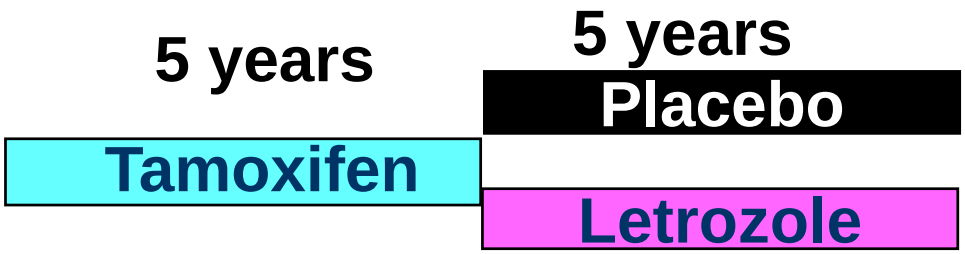


- **Tamoxifen demonstrated higher rates of endometrial cancer, ischemic heart disease, and cerebrovascular disease.**

Fisher et al. *J Natl Cancer Inst*. 2001;93:684.

Extended Adjuvant Therapy with AIs

MA 17 (5000pts)

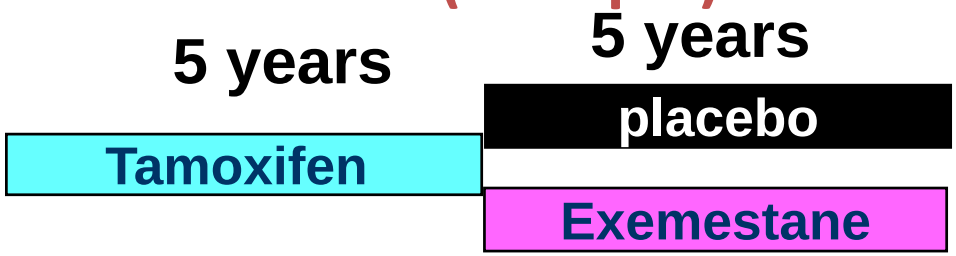


HR 0.58

4 Year DFS 4.6%

Goss et al. *JNCI* 2005

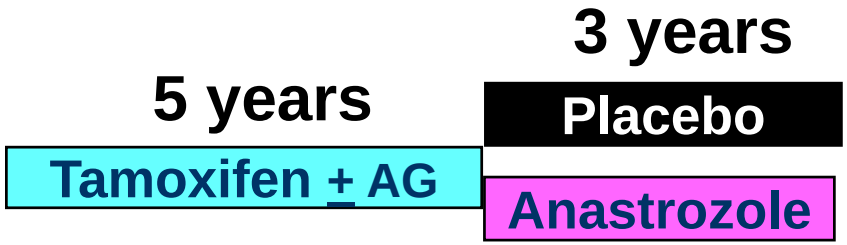
NSABP-B33 (1598pts)



0.44 p 0.004

Mamounas et al. *JCO 2008 26; 1965*

ABCSG-6a (856pts)

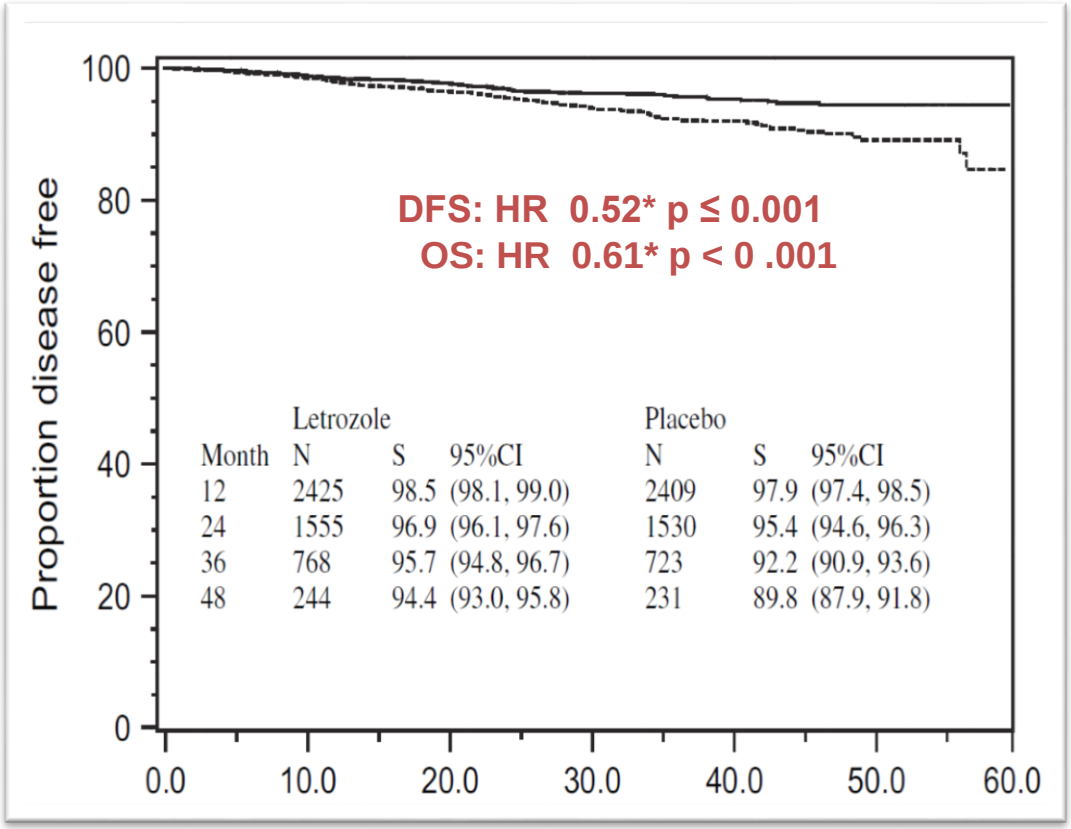


0.64 p 0.05

Update of Jakesz et al. *J Clin Oncol*. 2005;23(16S):10s.

Longer-Term Outcomes of Letrozole v. Placebo After 5 Years of Tamoxifen in the MA.17 Trial: Analyses Adjusting for Treatment Crossover

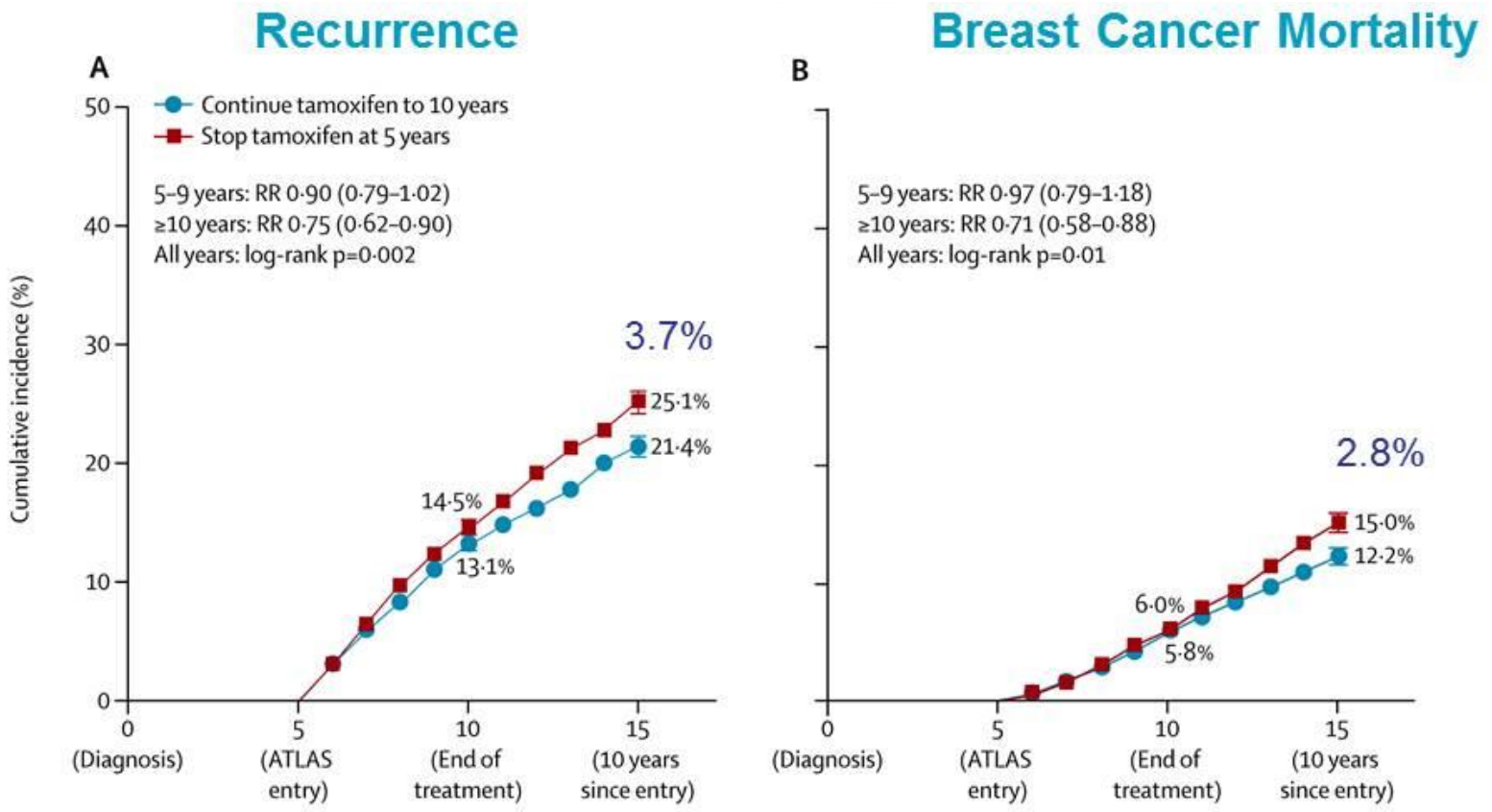
- Median FU 6.4 years
- 61% on placebo accepted cross over to letrozole
- Median time to cross over 2.7 years (range 1-7 years)



*IPCW: inverse probability of censoring weighted Cox model

Huan Jin,et al .J Clin Oncol 30:718-721. 2011

ATLAS: Adjuvant Tamoxifen 10 v 5 years n 6846 patients



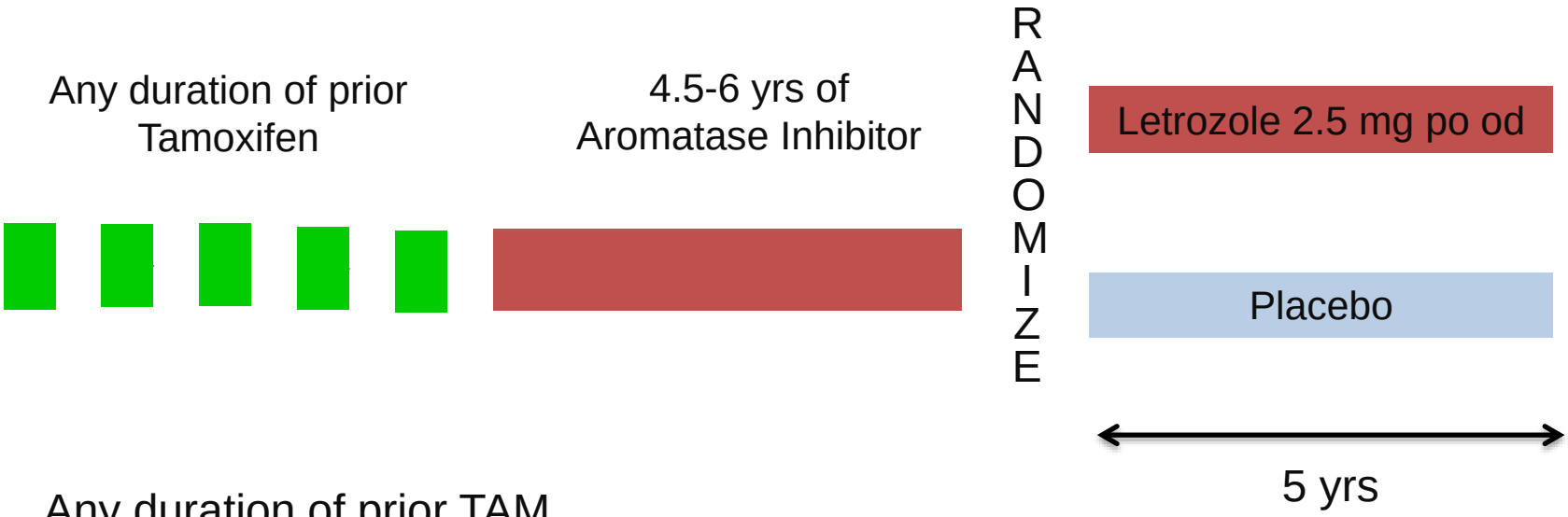
- **Gain independent of age (<55 v ≥55) or nodes**
- **Reduced overall mortality (639 *vs* 722 deaths, p=0.01)**
- **Non-breast cancer deaths nsd (RR 0.99)**

Davies C et al. Lancet 2013;381:805-16

MA.17R Trial Design

AI x 5 yrs - Following Prior 5 years of AI - preceded or not by Tamoxifen

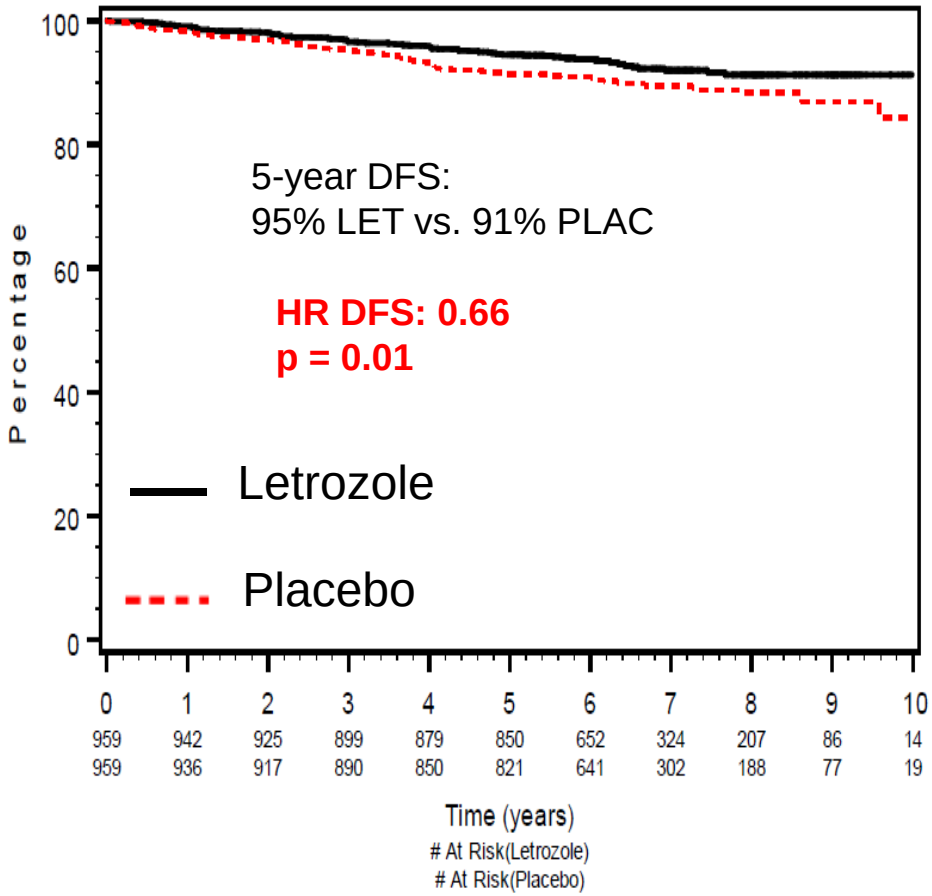
Oct 2004- May 2009



Any duration of prior TAM
54% N+ve
58% Adjuvant chemotherapy

Goss et al 2016. NEJM 375:209-19

MA.17R – Disease-Free Survival (Median FU 6.3 yrs)



	Let	Plac
Subjects who had a DFS event	67 (7.0)	98 (10.2)
Distant recurrence	42 (4.4)	53 (5.5)
Loco-regional recurrence	19	30
Bone	28	37
Contralateral breast cancer § CBC	13 (1.4)	31 (3.2)

Goss et al 2016. NEJM 375:209-19

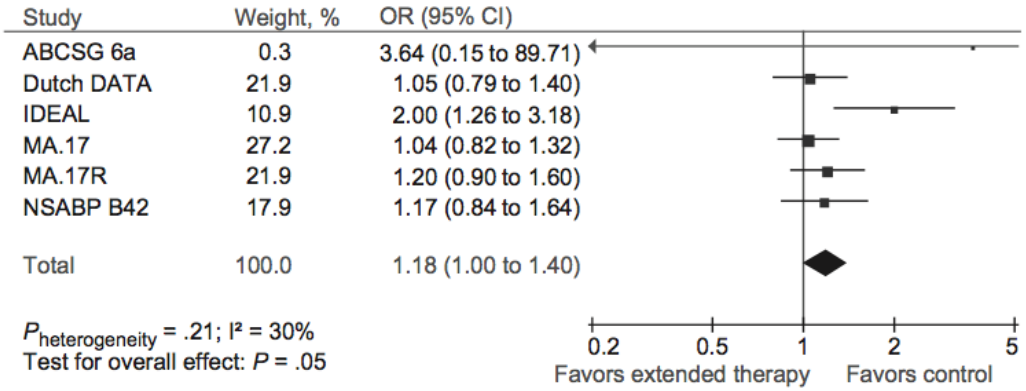
Further Trials of Extended Adjuvant AIs

	Initial ET	Treatment	n	FU (yrs)	DFS	Absolute Diff.	Significance
IDEAL[1]	AI±Tam 5yrs	Let x 2.5yr Let x 5yr	1824	6.6	84.7% 87.9%	3%	HR 0.96, p 0.70
NSABP B-42[2]	AI±Tam 5yrs	Let x 5 yrs Plac x 5 yrs	3966	6.9	84.7% 81.3%	3%	HR 0.85 p 0.048
ABCSG -16[3]	AI±Tam 5yrs	Ana x 2yr Ana x 5yr	3484	8.8	71.1% 70.3%	-0.8	HR 1.01 p 0.93
DATA[4]	Tam 2-3yrs	Ana x 6yr Ana x 3yrs	1912	4.1	83% 79%	4%	HR 0.79, p=0.07

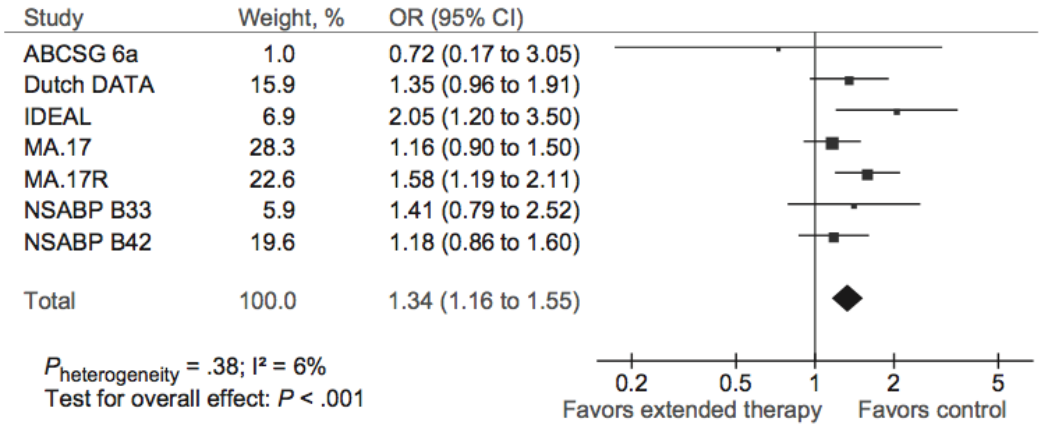
1. Blok et al. JNCI 2018 2. Mamounas et al., SABCS 2016
3.Gnant SABC 2017 4. Tjan-Heijnen et al., Lancet Oncol 2017

Toxicity of Extended Adjuvant AIs in Early Breast Cancer: A Systematic Review and Meta-analysis

Cardiovascular Events



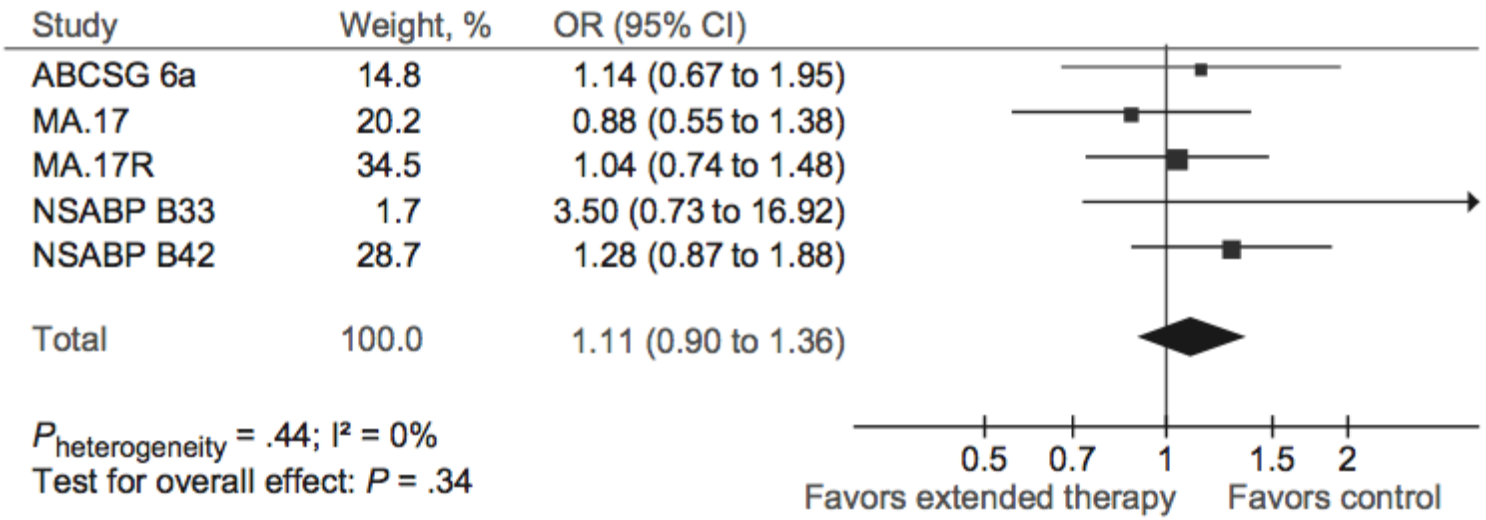
Bone Fractures



Goldwaser et al. JNCI 2018 110. No 1

Toxicity of Extended Adjuvant AIs in Early Breast Cancer: A Systematic Review and Meta-analysis

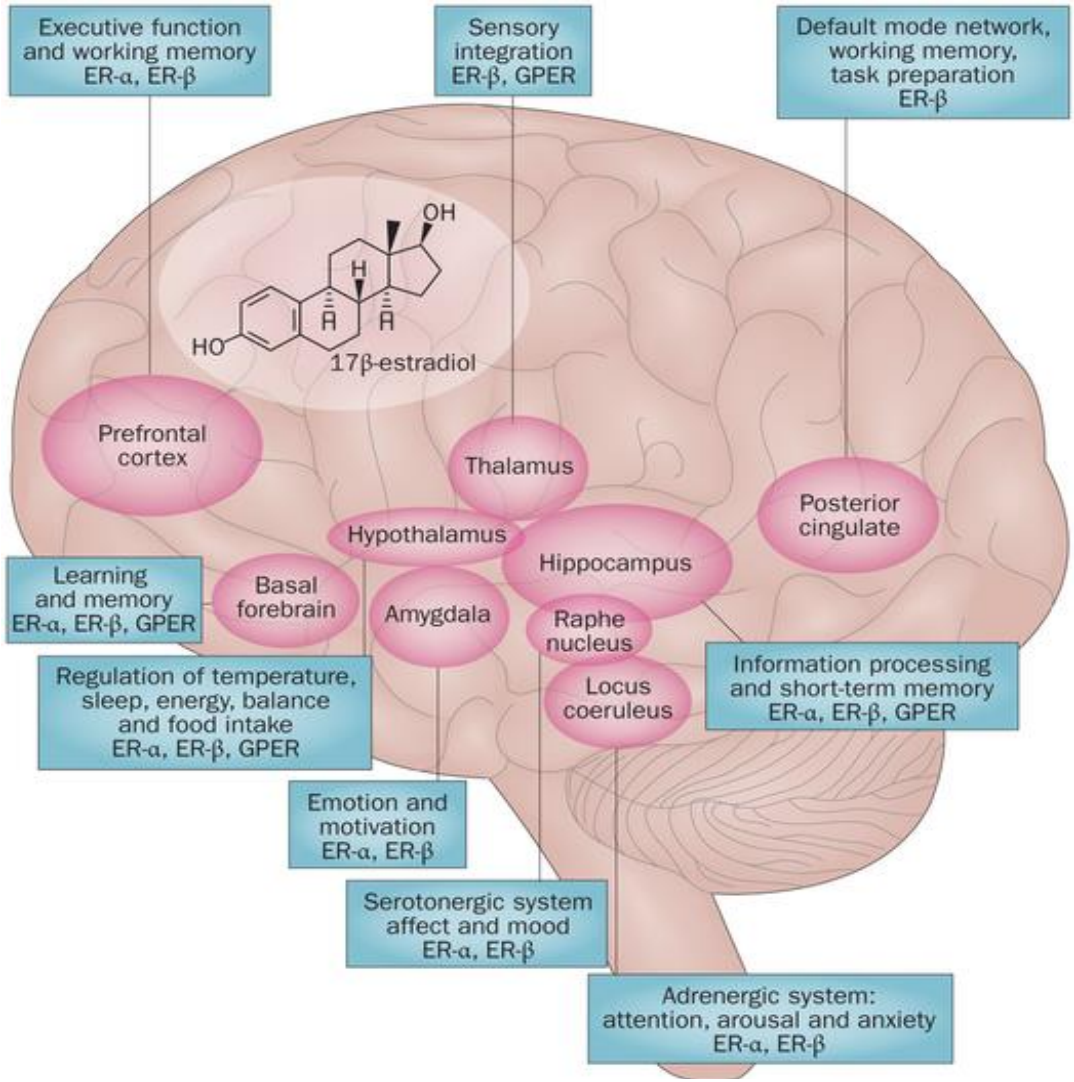
Non-Breast Cancer Deaths. - No Increase



Goldwaser et al. JNCI 2018 110. No 1

(2015)

Long Term Toxicities: Brain?



Brinton et al Nature Reviews Endocrinology 11, 393–405 (2015)

Question?

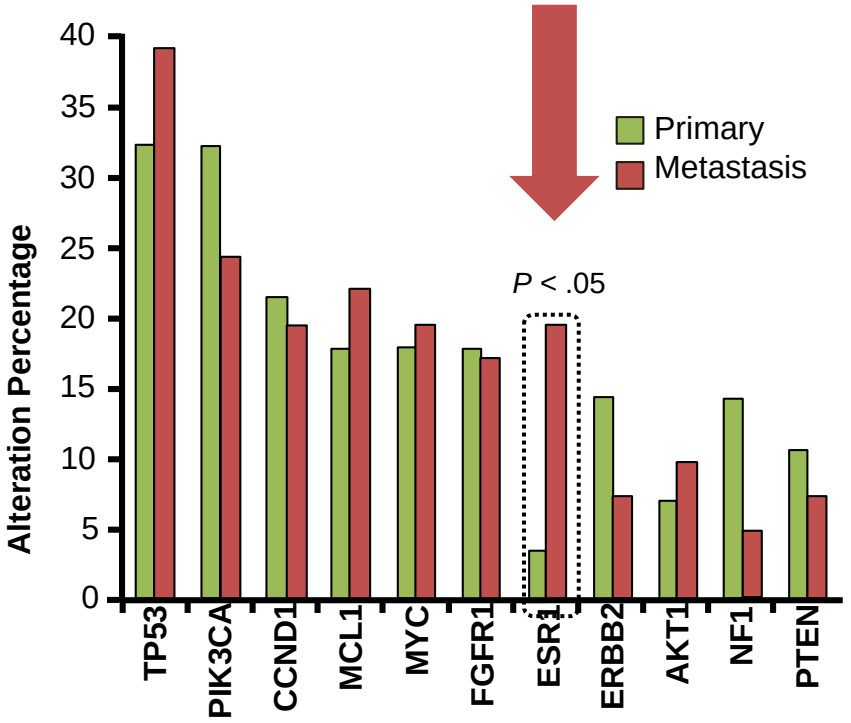
If the risk of late relapse persists so strikingly, why are extended use AIs beyond 5 years not more effective?

- Risk of late relapse may be falling?
- Bigger benefit may emerge with longer FU?
- Genomic mutations in the tumour?

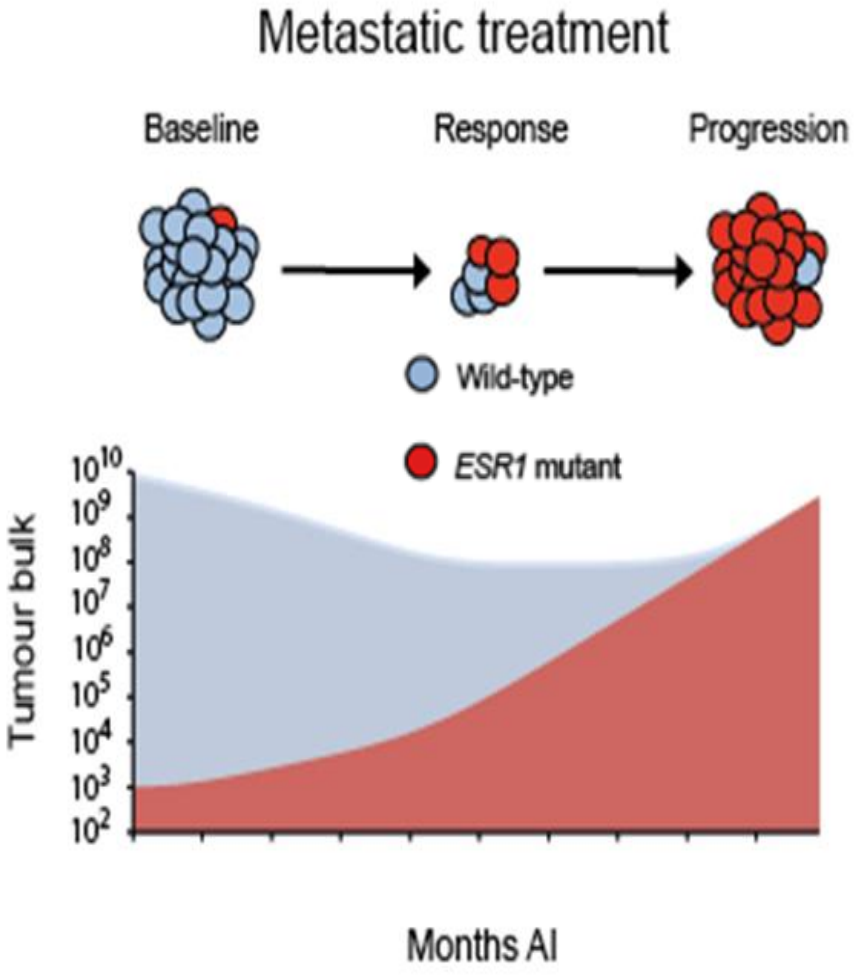
Can We Select Appropriate Endocrine Therapy on the Basis of Genomic Mutations?

Genomic Mutations in ER+ Advanced Breast Cancer. ESR 1

Genomic alterations in ER+ tumors

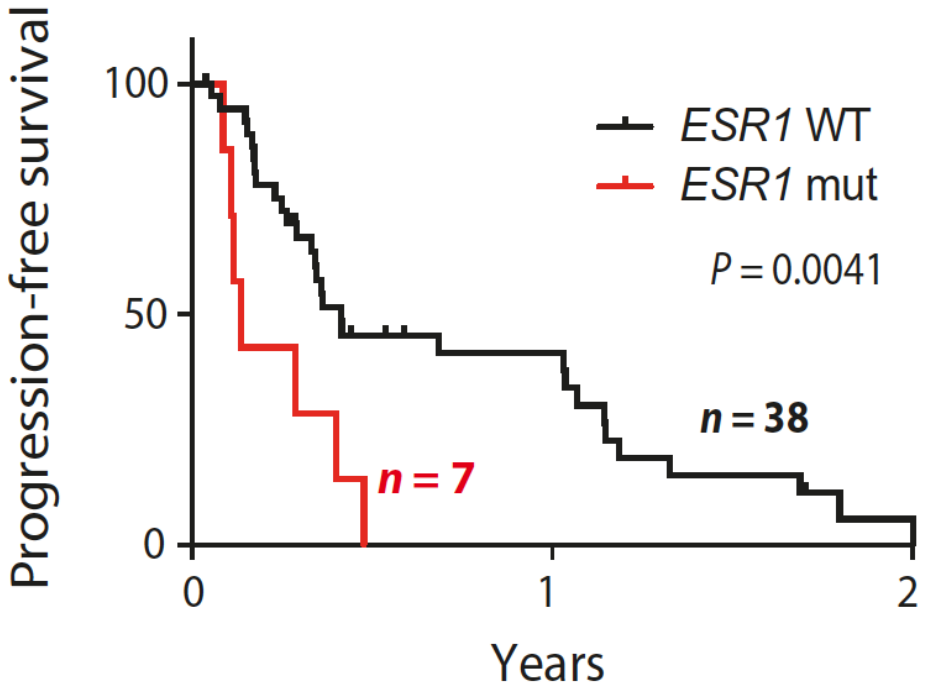


***ESR1* mutations occur in ~20% of endocrine resistant ER positive breast cancer**



Zhang Q.X et al. Cancer Res 1997 Li S et al. Cell Reports 2013 Toy W et al. Nat Gen 2013
Robinson DR et al. Nat Gen 2013 Merenbakh-Lamin K et al. Cancer Res 2013 Jeselsohn R et al. Clin Cancer Res 2014

ESR1 mutations in ctDNA Confer Resistance to Subsequent Aromatase Inhibitor



Retrospective single centre series
PFS on subsequent AI therapy

Schiavon *et al* AACR 2015, STM 2015

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Plasma *ESR1* Mutations and the Treatment of Estrogen Receptor–Positive Advanced Breast Cancer

Charlotte Fribbens, Ben O'Leary, Sarah Hrebien, Isaac Garcia-Murillas, Matthew Beaney, Mitch Dowsett, and Nicholas C. Turner, Institute of Cancer Research; Charlotte Fribbens, Ben O'Leary, Stephen R.D. Johnston, and Nicholas C. Turner,

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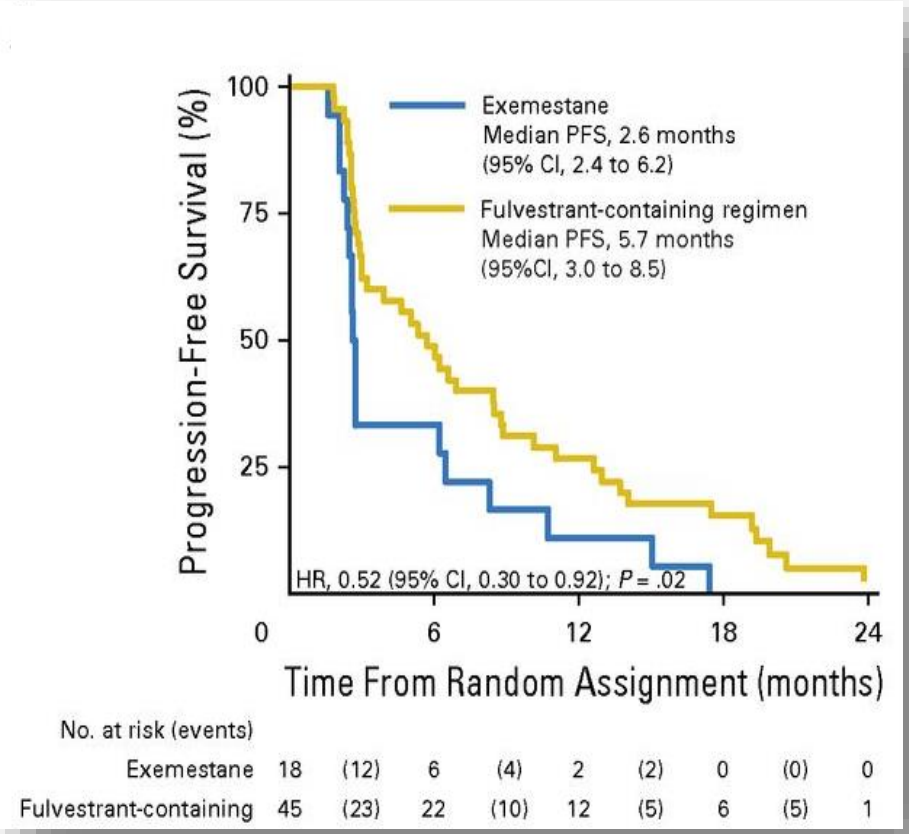
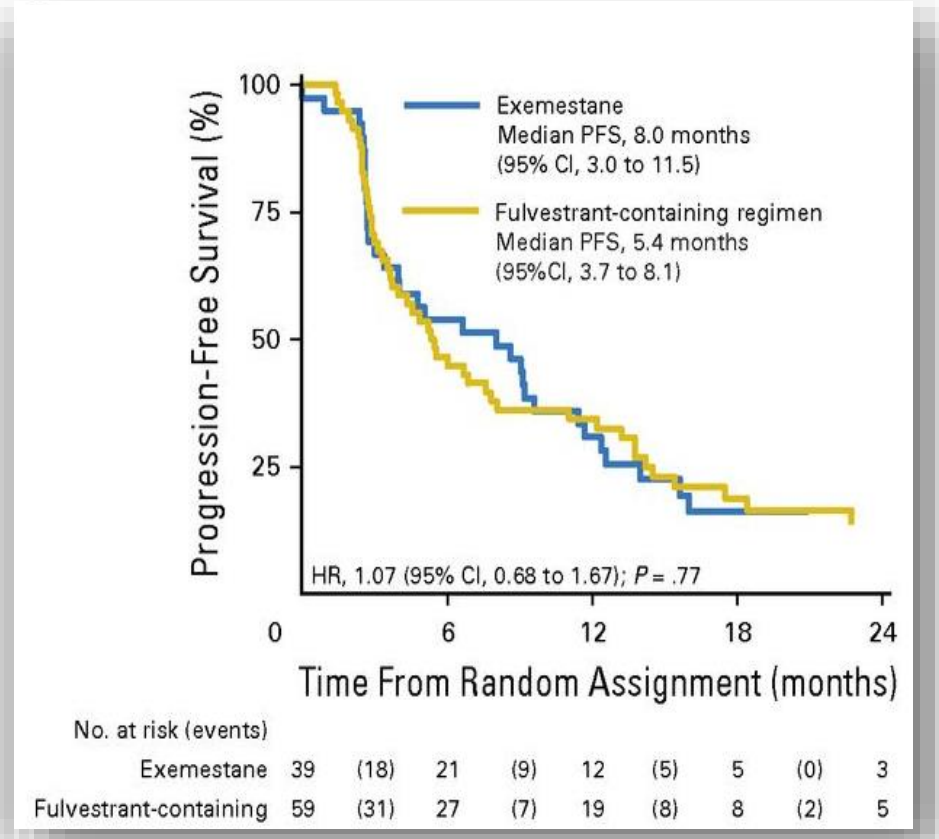
***ESR1* mutated**



***ESR1* wild type**

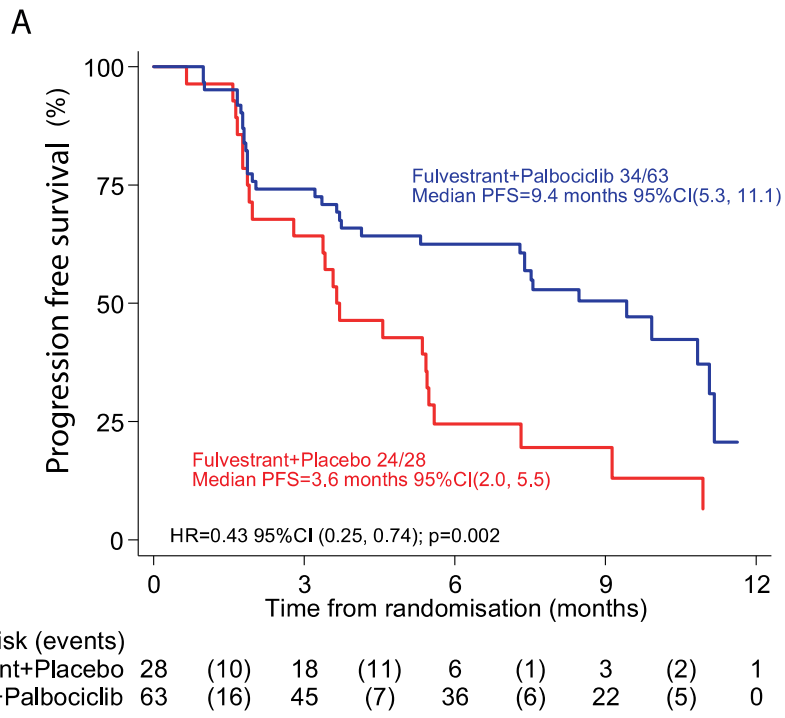


Fribbens C, et al. J Clin Onc. 2016;34(25):2961-8

PALOMA3 (Fulvestrant + Palbociclib) by *ESR1* mutation status

ESR1 Mutant (25%)

Fulvestrant-Palbociclib
Fulvestrant-Placebo



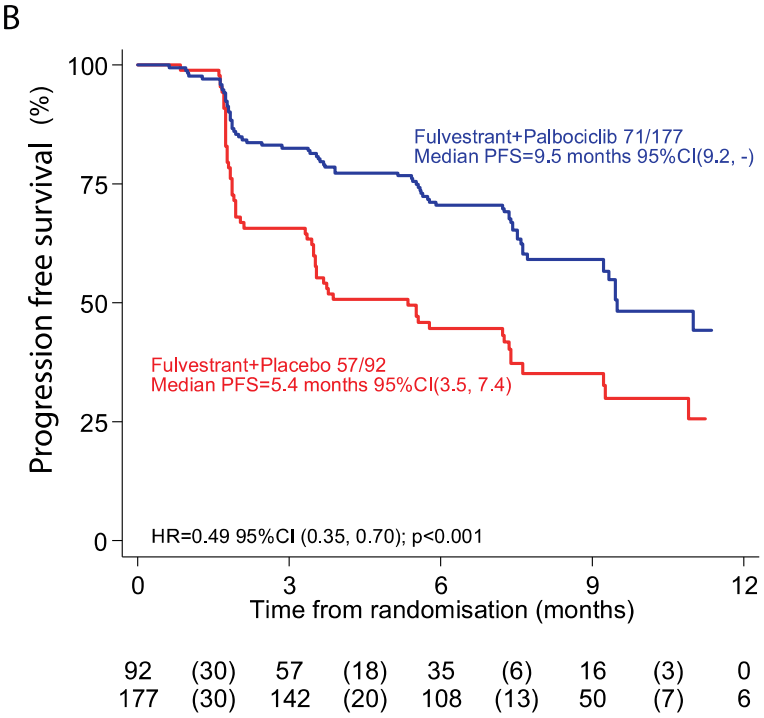
Number at risk (events)

Fulvestrant+Placebo	28	(10)	18	(11)	6	(1)	3	(2)	1
Fulvestrant+Palbociclib	63	(16)	45	(7)	36	(6)	22	(5)	0

HR = 0.43 95% CI 0.25 – 0.74, p = 0.002

ESR1 Wild type

Fulvestrant-Palbociclib
Fulvestrant-Placebo



	92	(30)	57	(18)	35	(6)	16	(3)	0
	177	(30)	142	(20)	108	(13)	50	(7)	6

HR = 0.49 95% CI 0.35 – 0.70, p < 0.001

O'Leary et al. AACR, 2016. Fribbens et al. *J Clin Oncol*, 2016

Hypothesis

- ESR-1 mutations are induced by AI exposure
- Fulvestrant overrides the mutation by degrading the receptor
- Palbociclib overrides the mutation by blocking a constitutively active ‘escape’ pathway
- Late relapses are likely to have a high incidence of ESR1 mutations
- They are therefore more likely to be controlled by fulvestrant or a CD4/6 combination therapy than by an AI alone

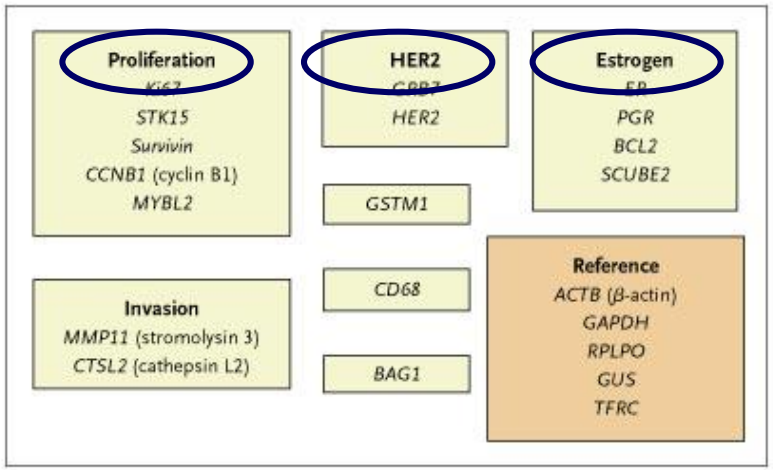
Conclusions (1)

- Late recurrence out to 20+years is a continuing risk in ER+ breast cancer
- Risk factors are the same as for early recurrence – nodes, size, grade
- Genomic platforms may help to predict – some appear better than others

Conclusions (2)

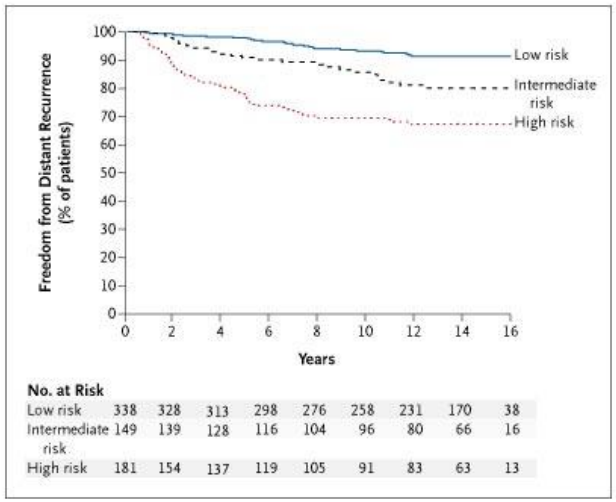
- An AI after tamoxifen significantly reduces the risk of late recurrence
- Tamoxifen for 10 years reduces the risk more than 5 years
- Continuing an AI for more than 5 years also reduces the risk, but only by a small amount
- Despite extended adjuvant endocrine therapy, the problem persists and new treatment strategies are required in selected patients

GHI 21-gene assay: Oncotype DX ™

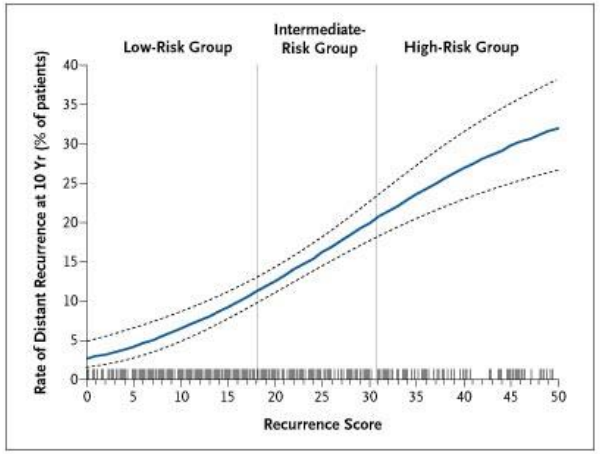


- 21 gene assay
- Formalin-fixed PE
- Based on B14 and B20
- N-ve ER+ve

Likelihood of distant recurrence according to recurrence score



Rate distant recurrence as continuous function of recurrence score



Paik et al NEJM 2004; 351;2817

- Could the theme of short term pre-operative treatment with molecular markers of response be scaled up for large scale phase 3 trials and for standard practice?

- How to design a large trial to answer this?

Ongoing Trials of Extended AI Adjuvant Therapy

Study	n	Treatment Pre-randomization	Arms at Randomization	Study number
MA.17R	1800	T (3-5 yr) → Any extended AI (5 yr) → 0-2 yr prior randomization	L (5 yr) vs placebo (5 yr)	NCT00754845
SALSA	3486	Any endocrine therapy (5 yr)	A (5 yr) vs A (2 yr)	NCT00295620
LEAD (Italian)	4050	T (2-3 yr)	L (5 yr) vs L (2-3 yr)	NCT01064635
DATA	1900	T (2-3 yr)	A (6 yr) vs A (3 yr)	NCT00301457
NSABP-B42	3966	AI or T-AI (5 yr)	L (5 yr) vs placebo (5 yr)	NCT00382070
SOLE	4800	Any endocrine therapy (5 yr)	L (5 yr) vs intermittent* L (5 yr)	NCT00553410

Abbreviations: A arimidex; AI aromatase inhibitor; L letrozole; LEAD Letrozole Adjuvant Therapy Duration trial; SALSA Secondary Adjuvant Long-term Study with Arimidex trial; DATA Different Durations of Anastrozole after Tamoxifen trial; SOLE Study of Letrozole Extension trial; n number; T tamoxifen; vs versus; yr year.

* intermittent: 48 months over 5 yrs: 4 x 9 months (9 mo followed by 3 mo treatment-free interval in yrs 1-4, -> 36 mo) plus 1 x 12 mo in yr 5 -> 48 months

Bone Toxicity During AI Treatment

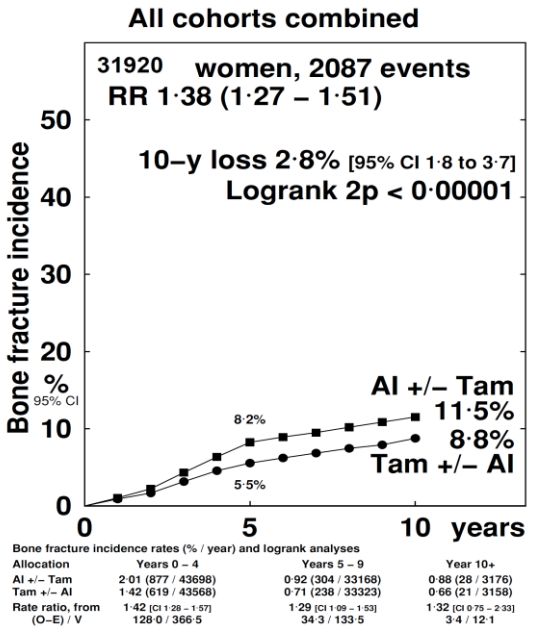
MA 17R data

Fractures	14% v 9%	p 0.001
New Onset Osteoporosis	11% v 6%	p<0.0001

EBCTCG metanalysis 2015

Increased fractures with AI during years 0-4 (RR 1.42, 1.28-1.57; p<0.0001)

Incidence remained higher in years 5-9 (RR 1.29, 1.09-1.53; p=0.003)
11.5% v 8.8%



Not big numerically, and preventable

Cardiovascular Toxicity with Adjuvant AIs

Cardiovascular Risk

AIs increased risk v tamoxifen (OR = 1.26, 95% CI: 1.10–1.43, *P* < 0.001)

Amir E,. JNCI 2011;103:1299–309

But tamoxifen is associated with a reduction in cardiovascular events

Grey AB, et al . J. Clin. Endocrin. And Met. 1995;80:3191–5.

Placebo controlled trials of AI (MA.17/BIG 1–97 and MAP3) no significant differences in cardiovascular events

Goss PE,, et al. NEJM 2011;364:2381–91.47,51

All cause overall survival improved

•Lipid Effects – MA17

•No significant difference in hypercholesterolaemia in MA 17

Goss PE, et al MA.17. JNCI 2005;97:1262–71

•In a substudy, no clinically meaningful alteration in lipid profile with letrozole

Wasan et al Oncol Ann 2005 16;707-15

Conclusions
How Should Clinicians React to MA-17R?

- For a small but important subgroup of women there is a continuing risk of relapse up to at least 15 years after diagnosis
- A small (3.2%) but significant group of patients have improved DFS with 10 yrs of treatment with an AI compared with 5, usually after tamoxifen.
- No major toxicities have emerged even with this very prolonged treatment
- BUT…
- A reduction in contralateral breast cancer contributes significantly to the DFS benefit. Difference is only 1.1% for distant recurrence
- There is so far no significant survival benefit.

Conclusions (2)

- The View of the Clinical Scientist
- We need to develop an algorithm based on both clinical and genomic parameters (eg ROR) for risk of very late relapse, so that the great majority of patients who don't need prolonged therapy can be identified

- The View of the Pragmatic Clinician (And many patients)
- NO subgroup has yet been identified with NO risk of late relapse.
- Patients on long term AIs have generally long since thrown off unpleasant early side effects
- So what's the downside of carrying on?

End