Extended Adjuvant Endocrine Therapy in Breast Cancer

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SEP 19

Overview

- Rationale
- Evidence
- Application to Clinical Practice

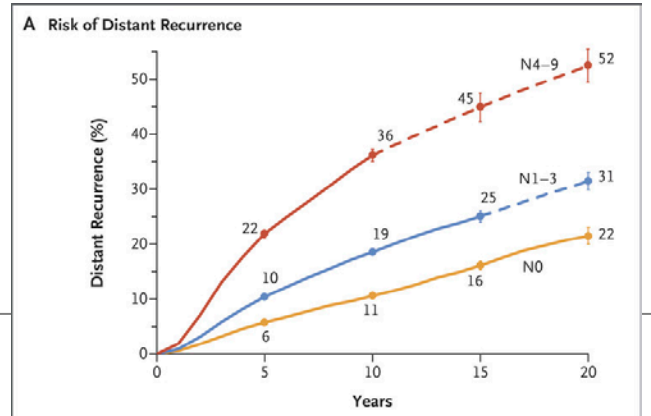
Rationale

1998: Early Breast Cancer Trialists Collaborative Group, meta-analysis of adjuvant tamoxifen use

- 37,000 women, 55 trials
- Tamoxifen use associated with an improvement in survival throughout the first 10 years

2017: EBCTCG, meta-analysis '20 year risk breast cancer recurrence after stopping endocrine therapy at 5 years'

- risk of distance recurrence after 5 yrs adjuvant endocrine continues for at least subsequent 15 years
- Strongly correlated with nodal status and T size

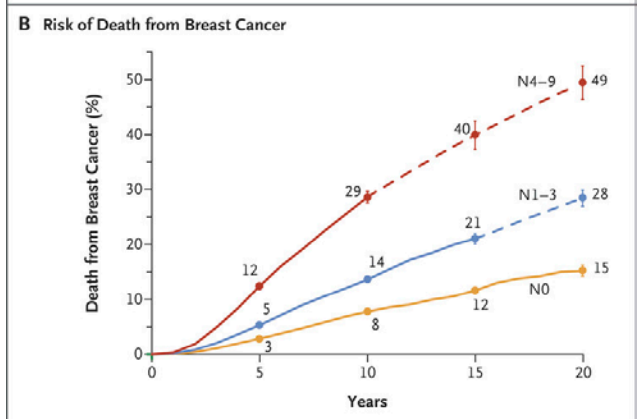


No. at Risk

N4–9	12,333	8,116	2165	259	52
N1–3	31,936	23,576	7250	949	183
N0	29,925	24,081	8571	1982	414

No. of Events — annual rate (%)

N4–9	2568 (4.8)	969 (4.0)	121 (3.1)	13 (2.2)
N1–3	3126 (2.2)	1421 (1.9)	241 (1.7)	39 (1.8)
N0	1646 (1.2)	835 (1.1)	272 (1.3)	68 (1.4)

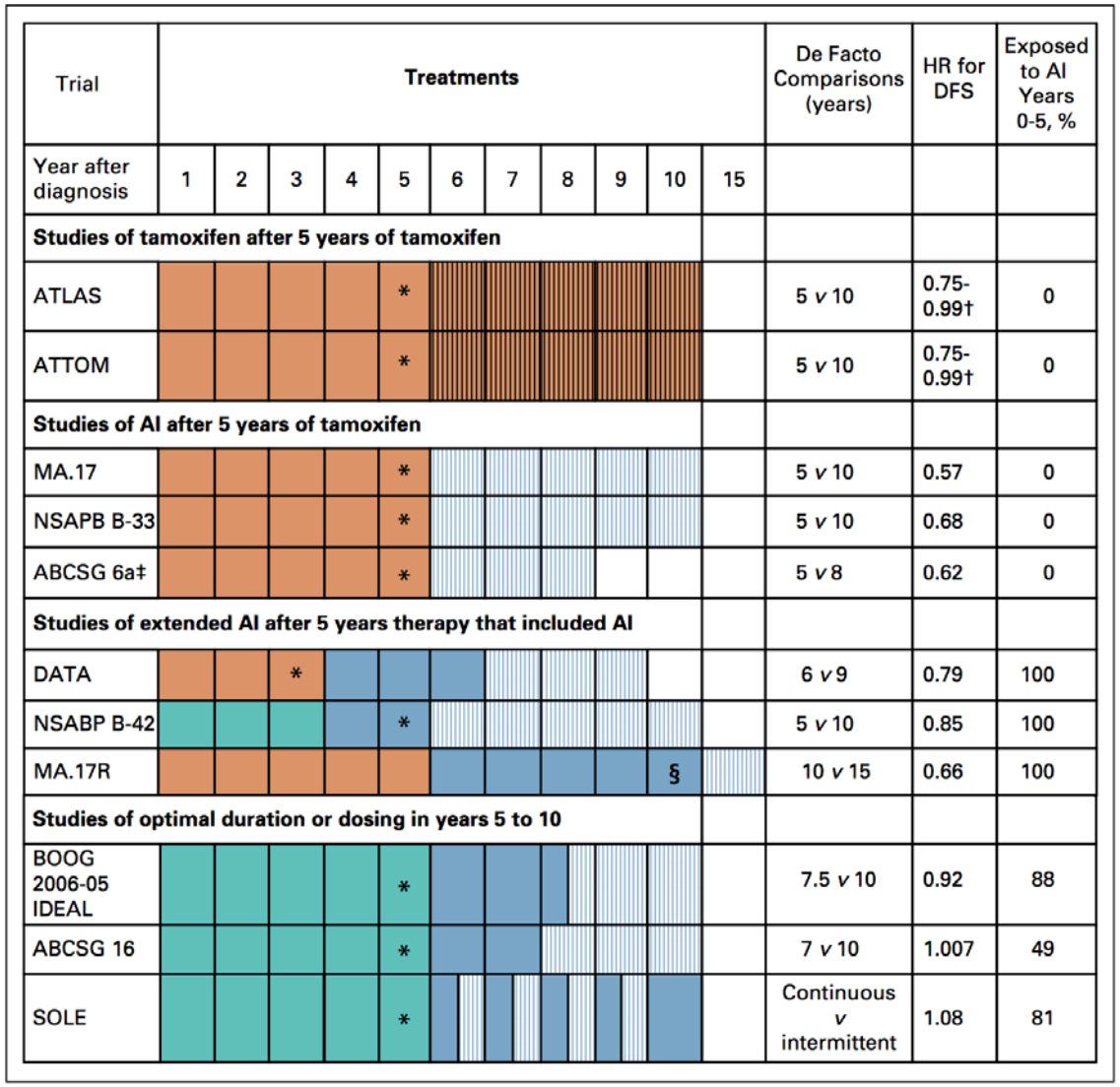


No. at Risk

N4–9	12,333	9,079	2481	294	57
N1–3	31,936	24,866	7728	1011	197
N0	29,925	24,819	8926	2144	476

No. of Events — annual rate (%)

N4–9	1463 (2.6)	1154 (4.1)	185 (3.7)	20 (2.3)
N1–3	1600 (1.1)	1506 (1.9)	319 (1.9)	52 (1.8)
N0	826 (0.6)	890 (1.0)	228 (0.8)	77 (1.0)



Trial	Treatments											De Facto Comparisons (years)	HR for DFS	Exposed to AI Years 0-5, %
Year after diagnosis	1	2	3	4	5	6	7	8	9	10	15			
Studies of tamoxifen after 5 years of tamoxifen														
ATLAS					*							5 *v* 10	0.75-0.99†	0
ATTOM					*							5 *v* 10	0.75-0.99†	0
Studies of AI after 5 years of tamoxifen														
MA.17					*							5 *v* 10	0.57	0
NSAPB B-33					*							5 *v* 10	0.68	0
ABCSG 6a‡					*							5 *v* 8	0.62	0
Studies of extended AI after 5 years therapy that included AI														
DATA			*									6 *v* 9	0.79	100
NSABP B-42					*							5 *v* 10	0.85	100
MA.17R										§		10 *v* 15	0.66	100
Studies of optimal duration or dosing in years 5 to 10														
BOOG 2006-05 IDEAL					*							7.5 *v* 10	0.92	88
ABCSG 16					*							7 *v* 10	1.007	49
SOLE					*							Continuous *v* intermittent	1.08	81

Overview of Trials

Key:

- * Time of randomization
- **Orange**: tamoxifen
- **Teal**: tamoxifen or AI
- **Blue**: AI
- **Striped**: timing of intervention or placebo or no treatment
- *NB- in MA.17R patients were randomized after 5 years of letrozole. The majority, but not all, had also received 5 years of tamoxifen*

Extended Tamoxifen 5vs 10

ATLAS (USA); n=12800 (n=6800 ER +), 1:1 randomised 10 years tamoxifen or stop.

Recruitment 1996-2005

Published 2012

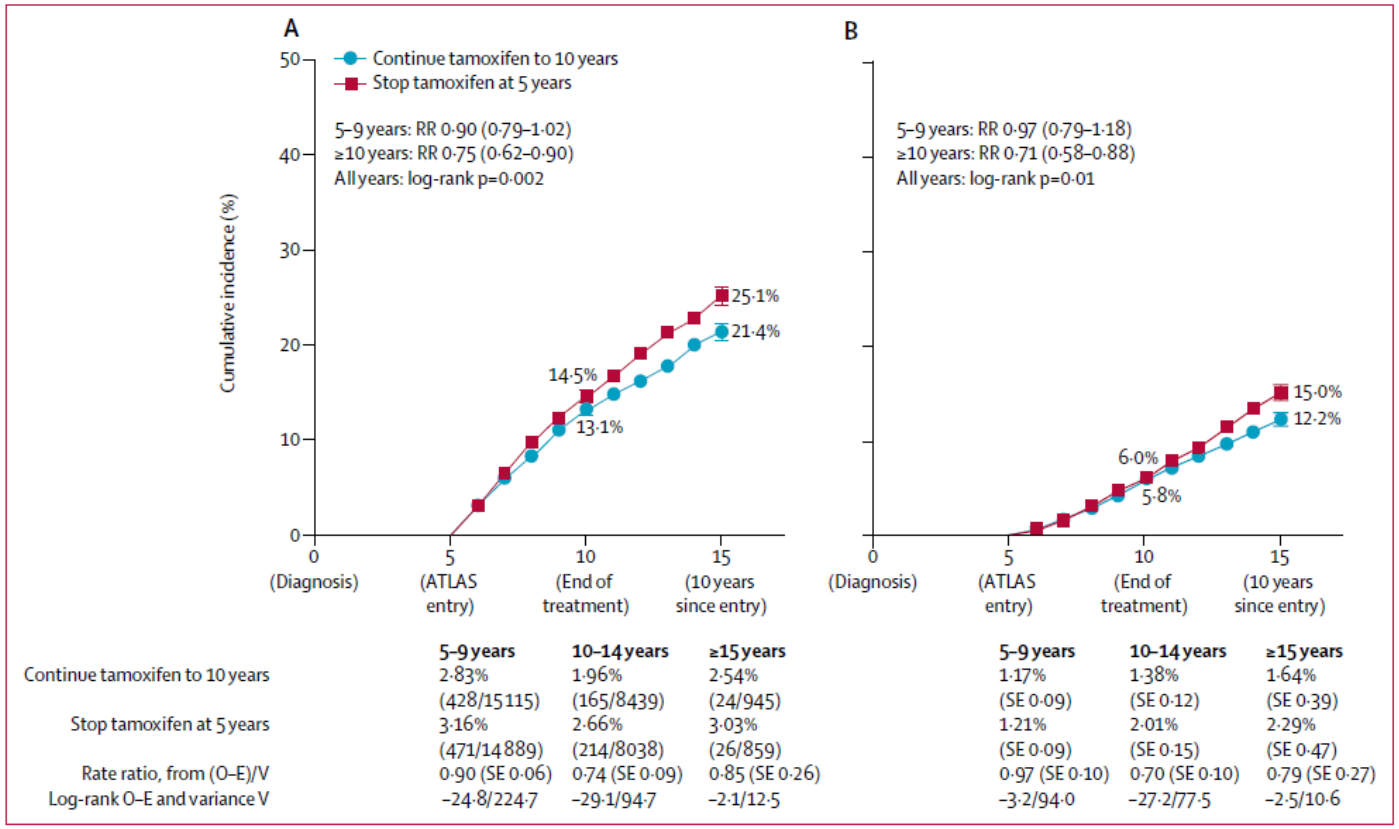
52% node neg

Good compliance

ATTOM (UK); n= 7000, ER+ve, 1:1 randomised 10 years tamoxifen or stop

- Recruitment 1991- 2005
- Published 2013
- 53% node neg, 31% node positive

Extended Tamoxifen: ATLAS



	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15115)	1·96% (165/8439)	2·54% (24/945)	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	3·16% (471/14889)	2·66% (214/8038)	3·03% (26/859)	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	−24·8/224·7	−29·1/94·7	−2·1/12·5	−3·2/94·0	−27·2/77·5	−2·5/10·6

Figure 3: **Recurrence (A) and breast cancer mortality (B) by treatment allocation for 6846 women with ER-positive disease**
Bars show SE. Recurrence rates are percentage per year (events/patient-years of follow-up). Death rates (overall rate–rate in women without recurrence) are percentage per year (SE). ATLAS=Adjuvant Tamoxifen: Longer Against Shorter.

ATLAS

Recurrence during years 5-14:
21.4% vs 25.1% (-3.7%)

Breast cancer mortality during years 5-14: **12.2% vs 15% (-2.8%)**

Extended Tamoxifen: ATTOM

- Further reductions in recurrence after year 7 (**HR 0.84** [0.73-0.95] during years 7-9, and **0.75** [0.66-0.86] later)
- Reduction in Breast cancer mortality after year 10 (**HR 0.77** [0.64-0.92]) with 10 years of tamoxifen

Overall Pooled Analysis:

- 5 year tamoxifen reduces breast cancer death rate by 33% @ 15ys

10 years tamoxifen reduces breast cancer death rate by further 25% after 10 year mark

Compared to NO tamoxifen, 10 years reduces risk death 33% in first 10 year and then 50% subsequently

Extended Tamoxifen

BUT

Endometrial cancer risk doubled (1.3% @ 5 years vs 2.9% @ 10 years)

VTE risk significantly increased

Interpretation

- Benefit is real but modest and delayed

-Encouraging for premenopausal women

- What about post menopausal women?

AI after 5 years Tamoxifen

MA 17

- randomised to letrozole vs placebo for 5 yrs following completion of 5 yrs of tamoxifen

n= 5187

published 2006

NSABP B33

-randomised to exemestane vs placebo for 5 yrs following completion of 5 yrs of tamoxifen

n= 1598

Published 2008 after premature closure

ABCSG 6A

-randomised to anastrozole vs placebo for 3 yrs following completion of 5 yrs of tamoxifen (+/- the AI aminoglutethimide for first 2 years of tamoxifen)

- N=856
- Published 2007

AI after 5 years Tamoxifen: MA 17 Results

- **DFS HR 0.58** (95% CI 0.45-0.76, p<0.001)
- **Distant DFS HR 0.60** (95% CI 0.43-0.84, p=0.002)
- Biggest benefit seen in women who were premenopausal -> menopausal

- **OS in node +ve women HR 0.61** (95% CI 0.38-0.98, p=0.04) **First study to show survival advantage with an AI in early breast cancer **
- Reduced bone density in letrozole group but no significant difference in fracture risk

- BUT
- Closed early due to major effect at first analysis
- F/U just 30 months and patients allowed to cross over

AI after 5 years of Tamoxifen

Interpretation

-Confirms benefit of switch from Tam to AI for those who become post menopausal

- Greatest benefit seen in node positive

- But short follow up, ?long- term toxicity

what about those who were commenced on AI?

Extended AI beyond 5 years

MA 17R: extension MA17. Randomised to AI vs placebo after 5 years of AI (preceded by tamoxifen)

- n= 1918
- 46% node negative
- 20% no prior tamoxifen (n =400)
- 2016

AERAS: 5 years AI, continue vs stop for 5 years

- N= 1683
- Follow up 4.9 years
- San Antonio 2018

Extended AI: Results

MA 17R

- 5 year disease free survival rate **95% vs 91%**
- **OS = no difference**
- Significant reduction in Contralateral breast cancer
- Significantly **more** bone fractures
- QOL = same

AERAS

- 5 year disease free survival = **91.9% vs 84.4%**
- OS = 99% both groups
- All subgroups showed benefit
- More bone fractures (2.8% vs 1.1%)

Extended AI: Results

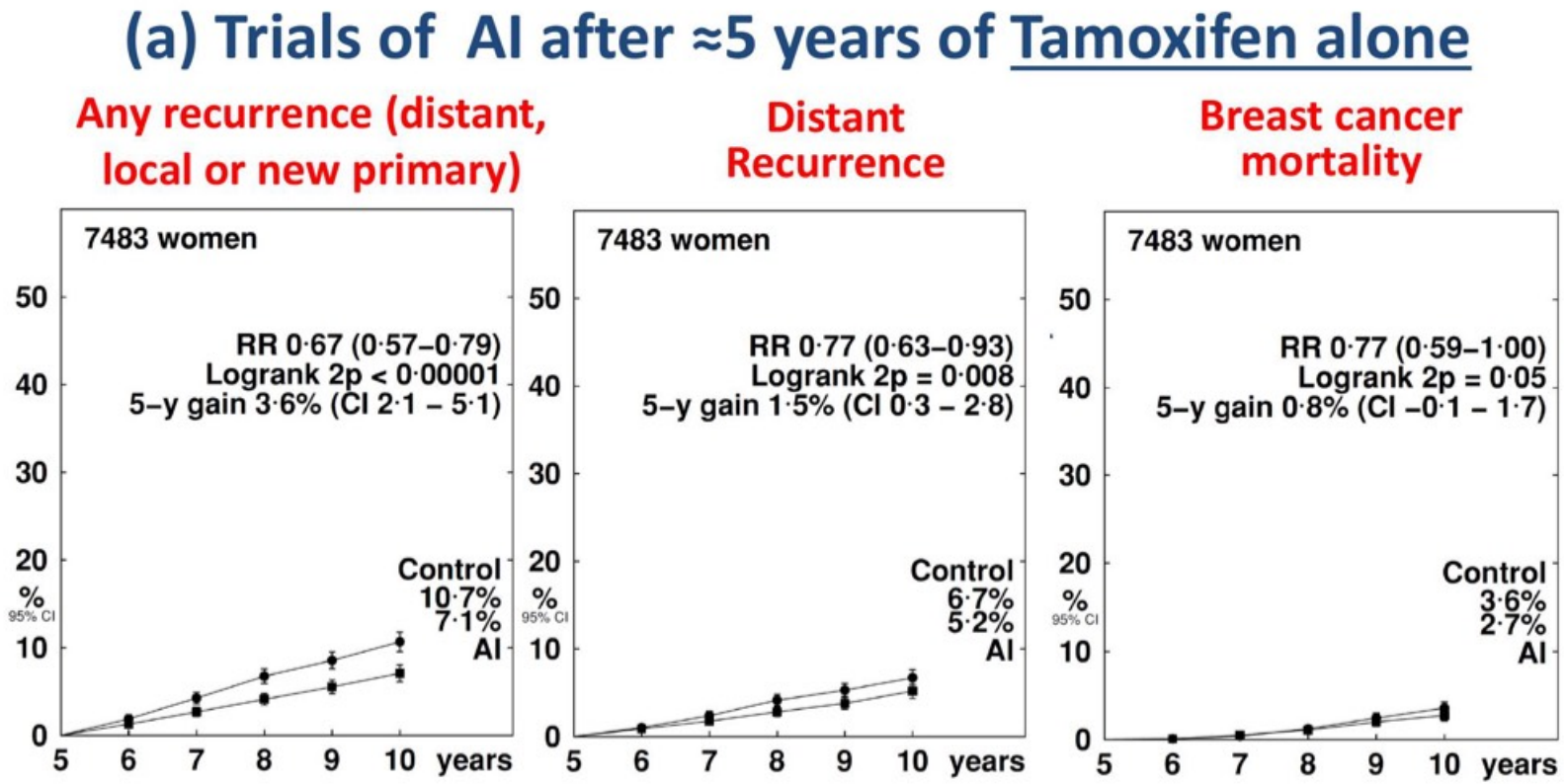
Interpretation

-Patients do very well

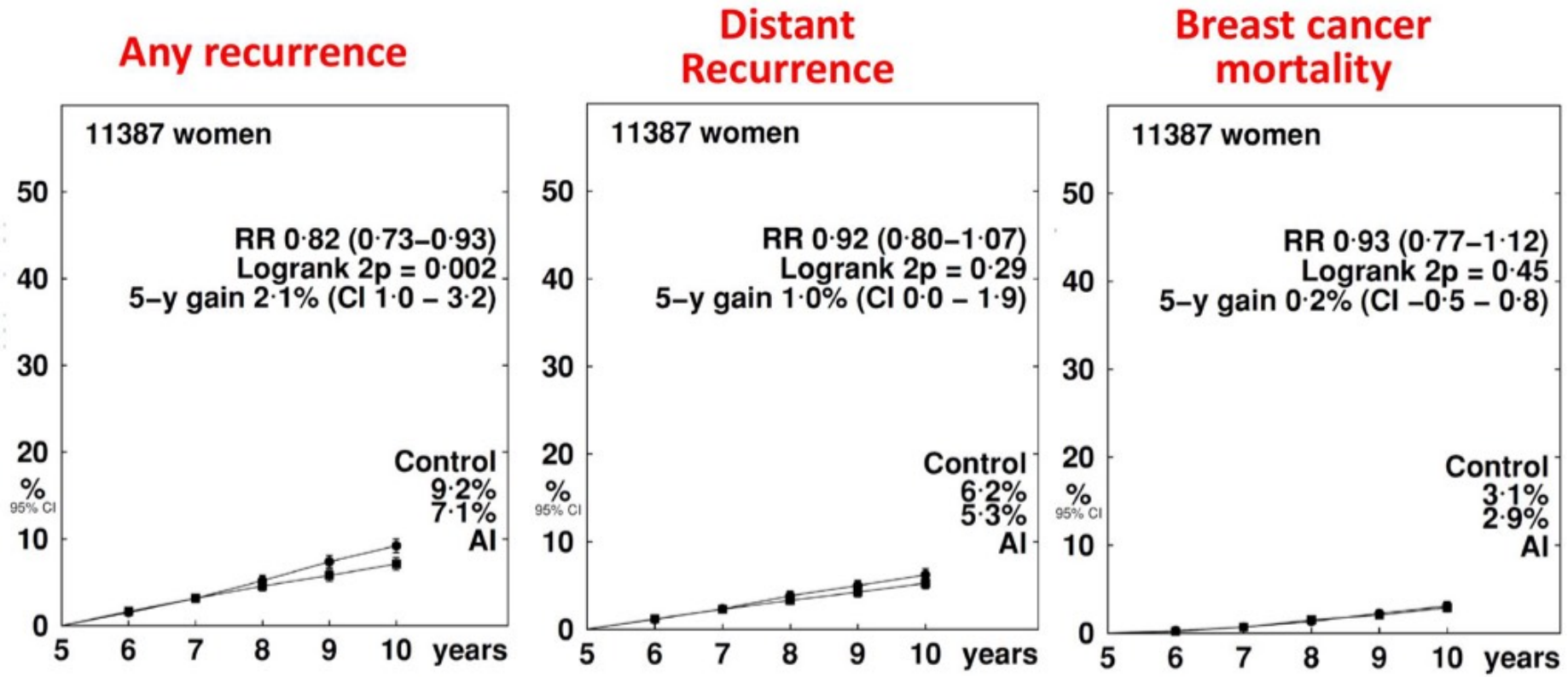
- Small but definite benefits at the cost of poorer bone health

Meta-analysis of Extended Endocrine

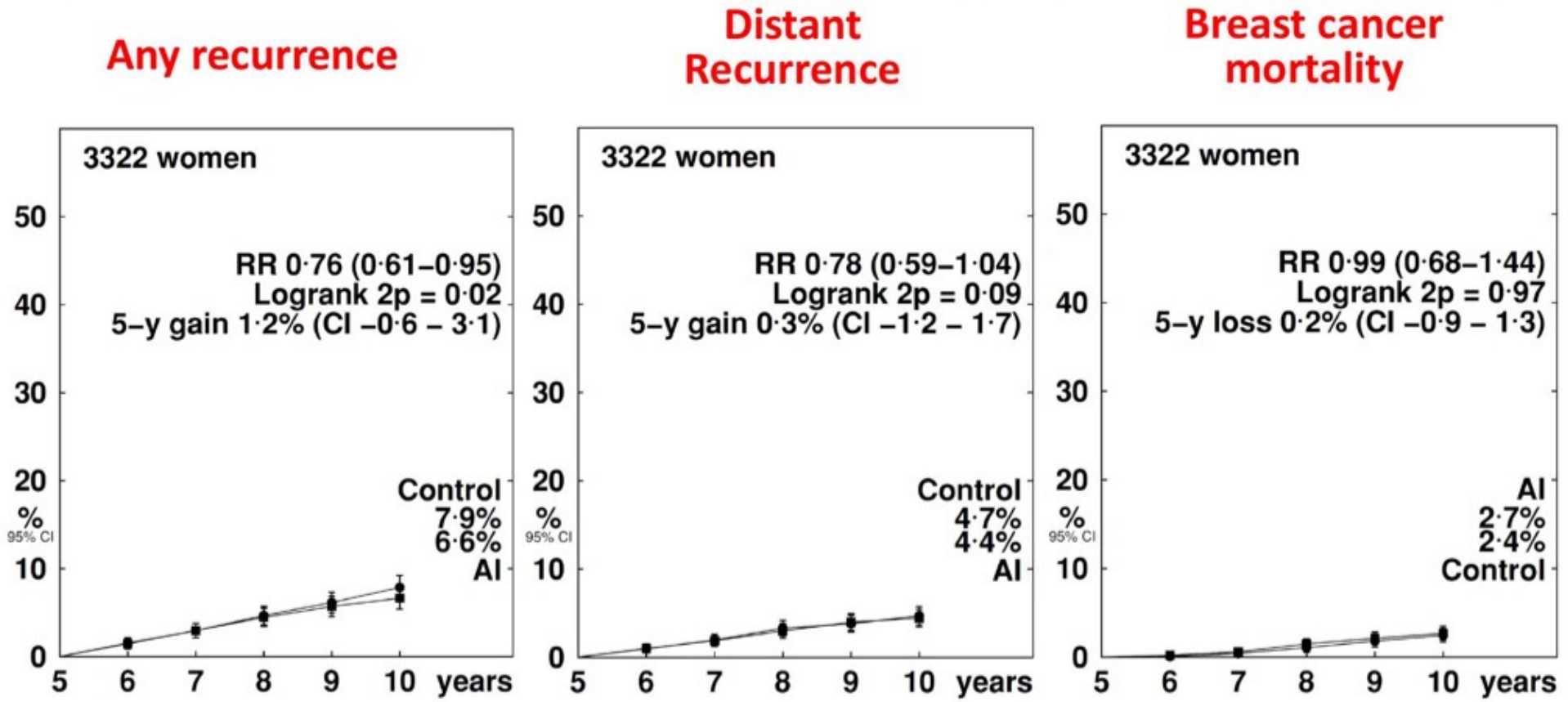
-Richard Gray, San Antonio 2018



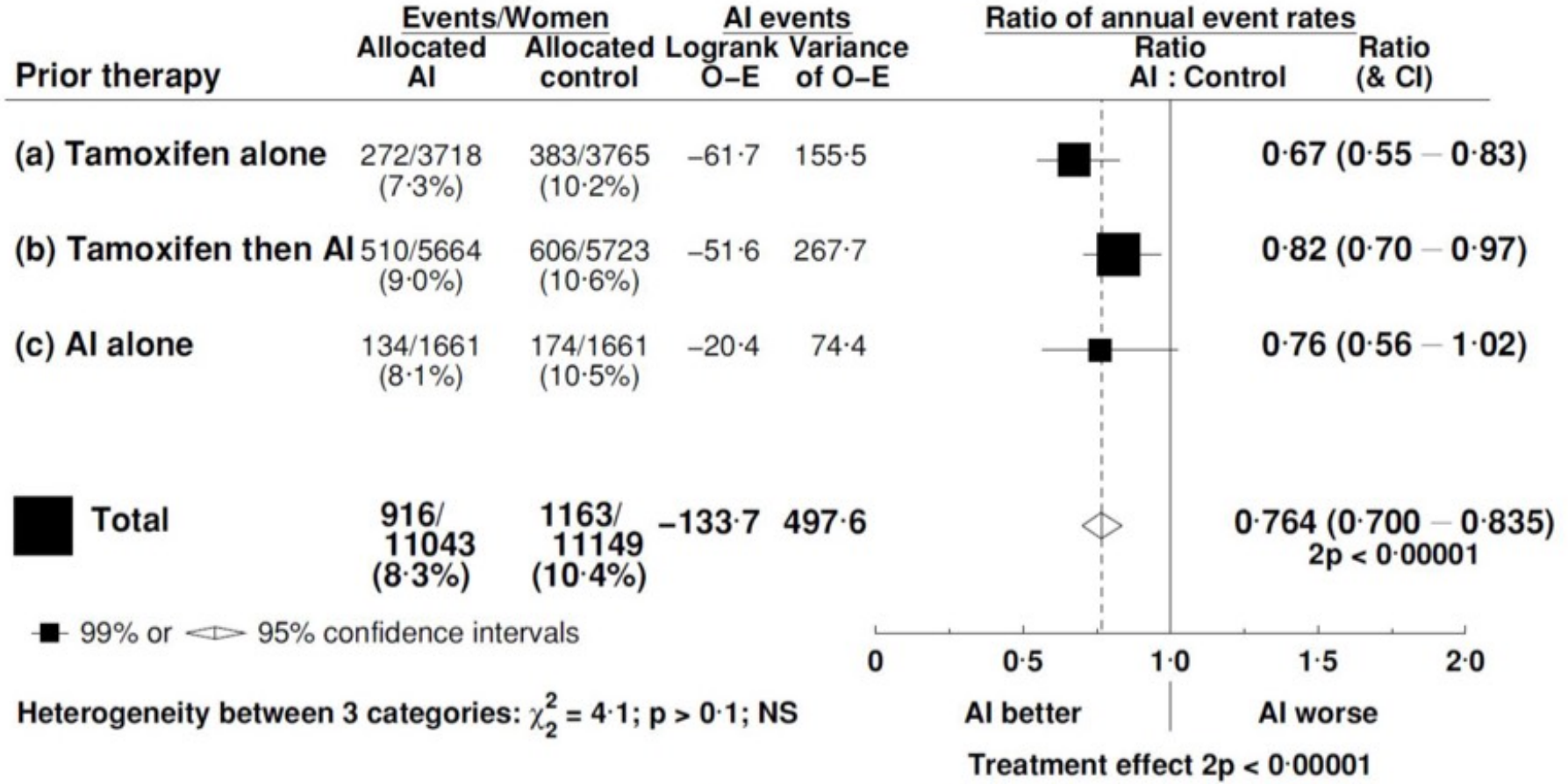
(b) Trials of Extended AI following 5-10 years of Tamoxifen then AI



(c) Trials of Extended AI following 5 years of AI alone

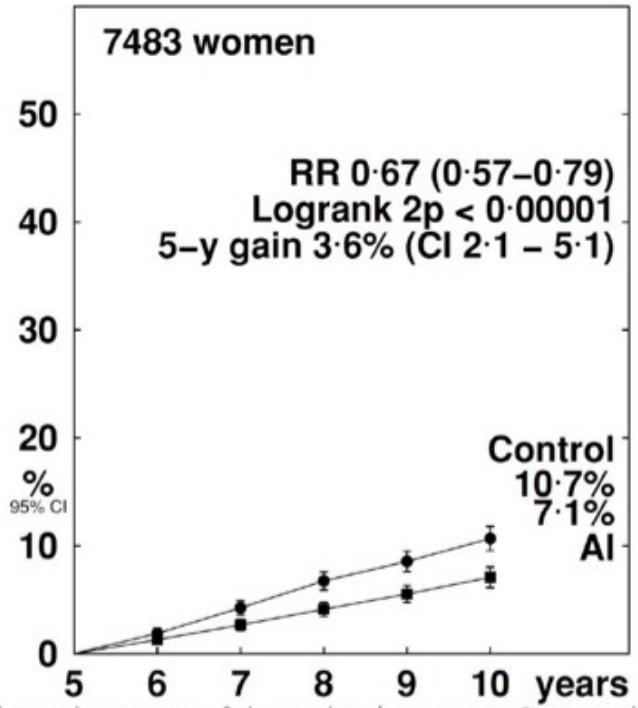


Effect on recurrence by prior endocrine therapy

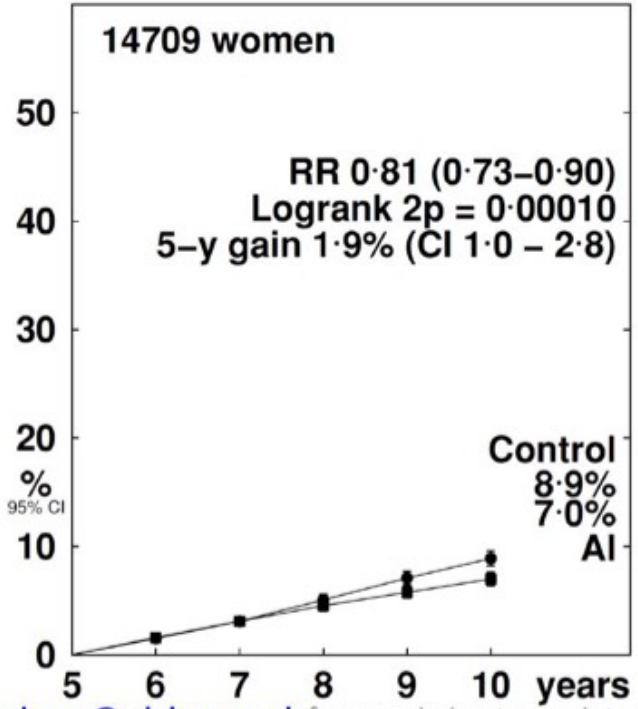


Summary: effect of extended AI therapy after 5-10 yrs on recurrence differs by type of prior endocrine therapy

Prior tamoxifen (a)



Prior AI (b + c)



Clinical Application

NCCN: ‘Consider extended endocrine’

ESMO: ‘Discuss with patients unless very low risk relapse. Optimal duration and regimen unknown. Only minimal benefit of AIs more than 5 years’

ASCO: ‘Recommended for node +ve patients. Consider for node negative along with established risk factors’

Clinical Application

High Risk: Extended endocrine

Low Risk: No extended endocrine

Intermediate: Discussion

Considerations:

- *Tolerance and Side effects*
- *Bone Health*
- *VTE risk*
- *Menopausal status*
- *Type of switch as to how long continue for*

Questions?