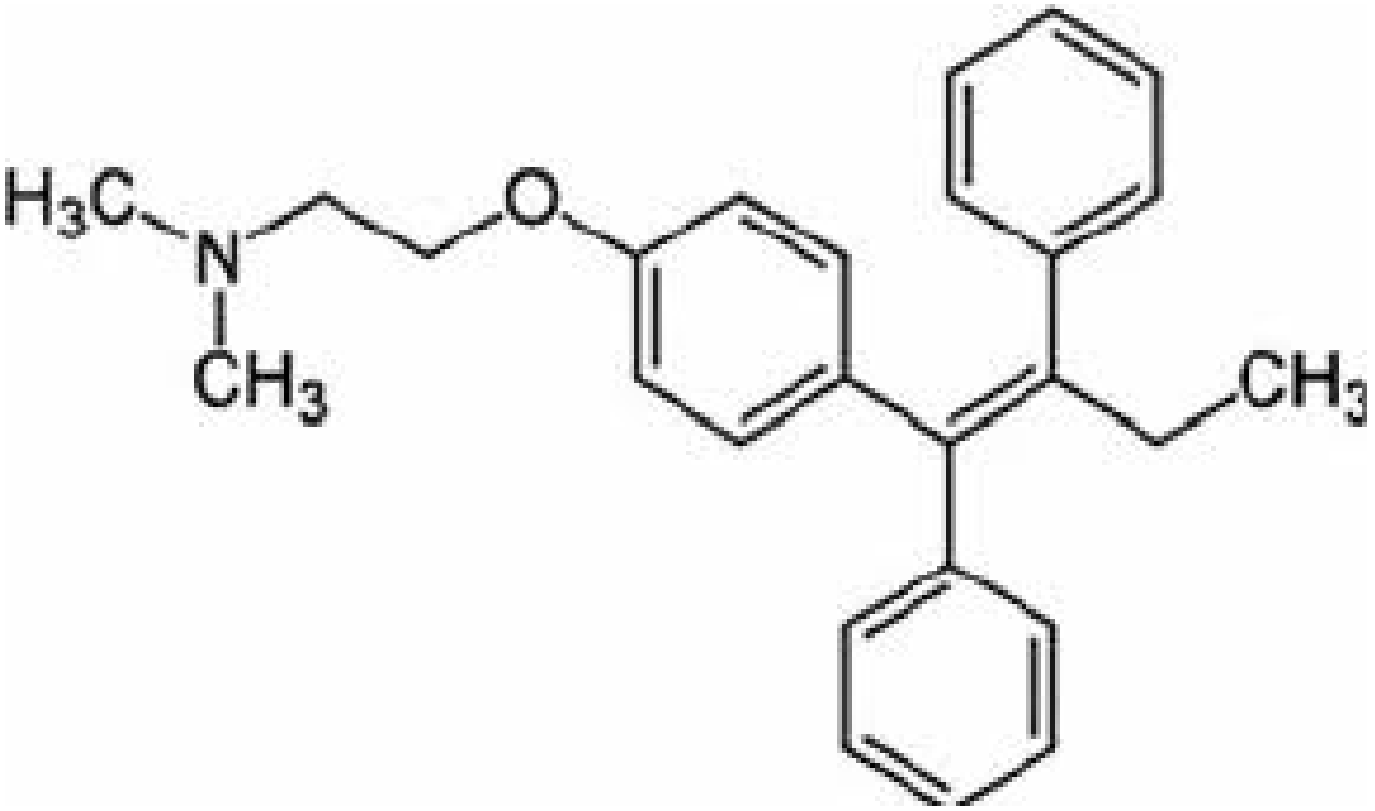
Five years of endocrine therapy as adjuvant for breast cancer

M Mccrystal

All because of work around an emergency contraceptive compound…….



Early dose and duration trials

- Earliest adjuvant studies initiated in 1970s
- 1-2 years vs nil – tamoxifen effective
- Mouse mammary tumour studies indicated tamoxifen likely cytostatic rather than cytotoxic- longer duration studies (Swedish, UK) 5 versus 2 years. Swedish OS HR 0.82 (0.69—0.99), n=3887. OS 10 years 80 vs 74%
- EBCCTG overview 1990 – 6 months - 5 years vs nil trend to favour longer duration

Tamoxifen

- EBCTCG meta-analysis 2011
  - 5 years of tamoxifen vs none in EBC

Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Summary

Background As trials of 5 years of tamoxifen in early breast cancer mature, the relevance of hormone receptor measurements (and other patient characteristics) to long-term outcome can be assessed increasingly reliably. We report updated meta-analyses of the trials of 5 years of adjuvant tamoxifen.

Methods We undertook a collaborative meta-analysis of individual patient data from 20 trials (n=21 457) in early breast

Lancet 2011; 378: 771–84
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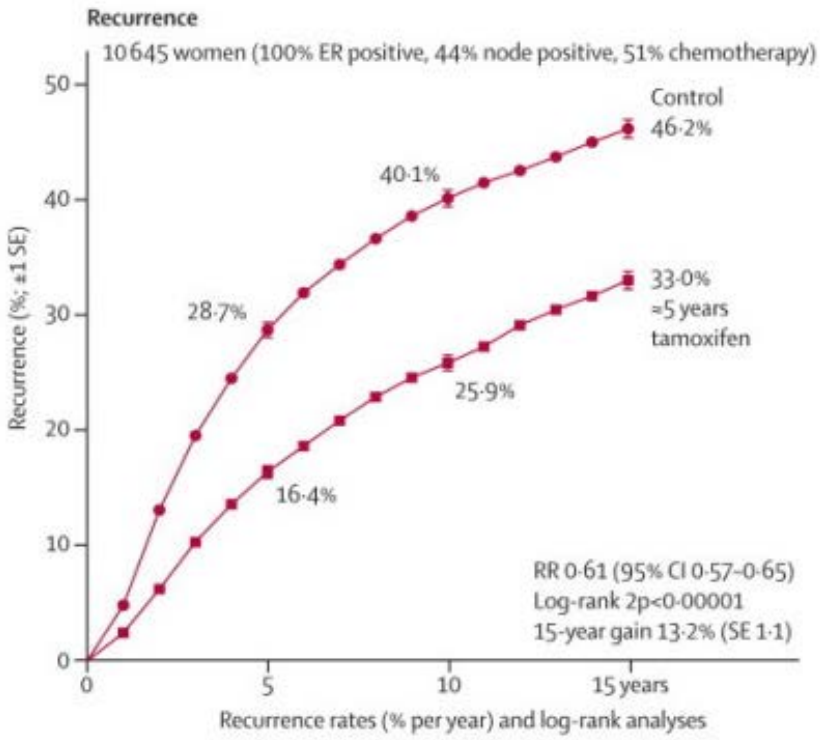
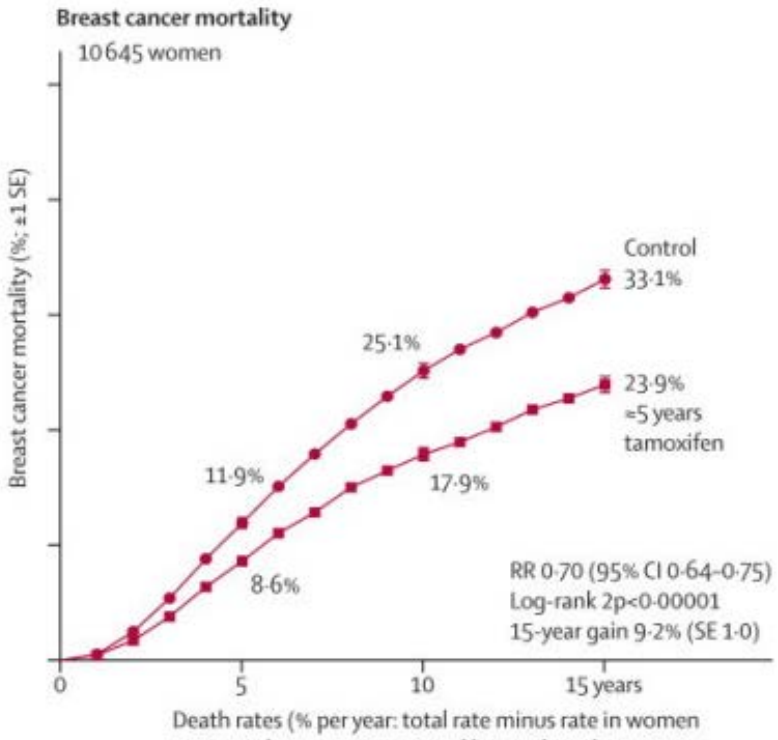
See Comment page 747

– Breast cancer recurrence 0.61 (CI 0.57-0.65)

– Breast cancer mortality 0.70 (CI 0.64-0.75)

Figure 5





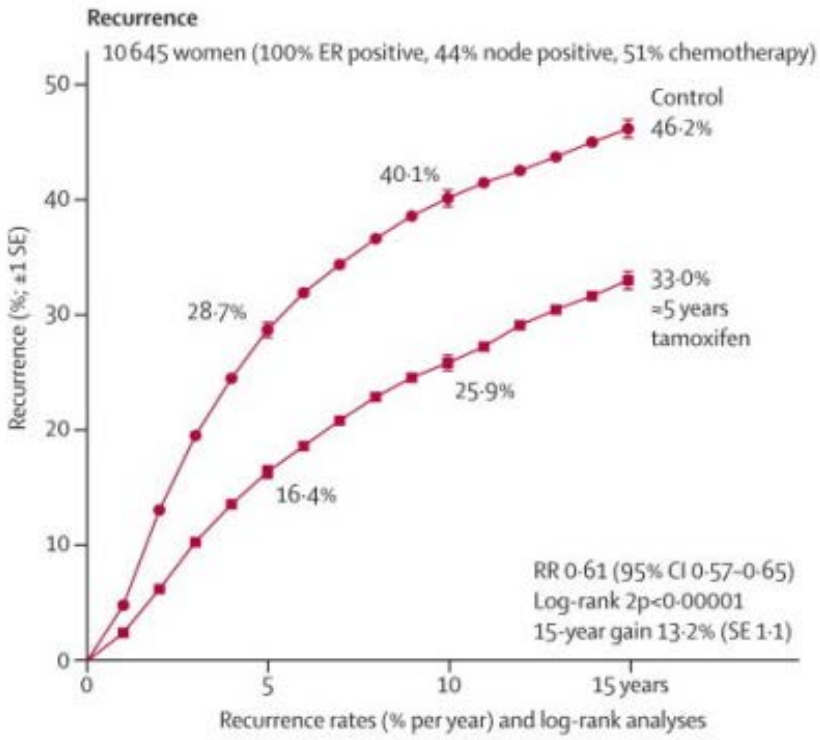
	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5

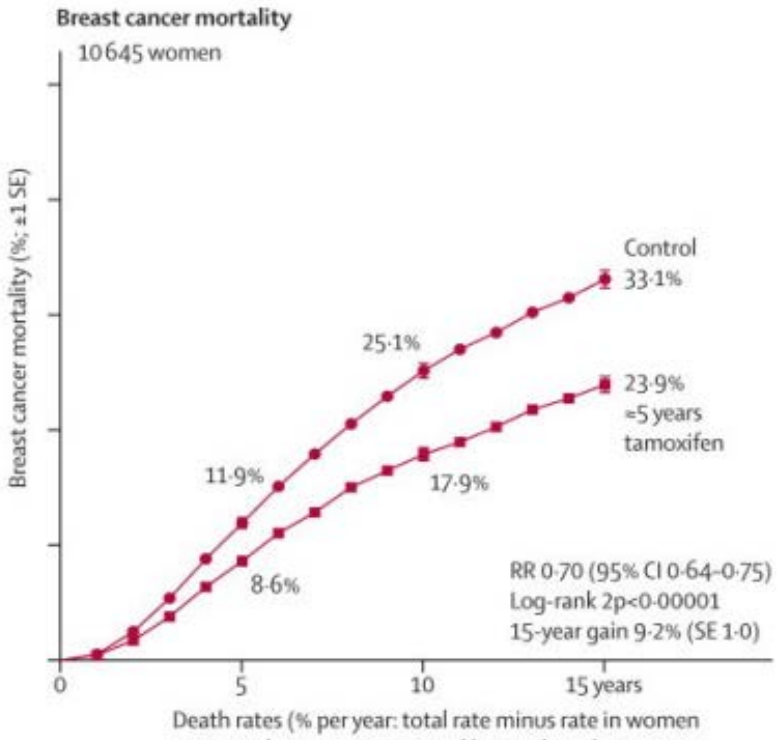
Years 0–4	Years 5–9	Years 10–14	Year 15+
1·79 (SE 0·08)	2·25 (SE 0·11)	1·54 (SE 0·11)	1·48 (SE 0·16)
2·46 (SE 0·10)	3·23 (SE 0·13)	2·28 (SE 0·14)	1·89 (SE 0·19)
0·71 (SE 0·05)	0·66 (SE 0·05)	0·68 (SE 0·08)	0·88 (SE 0·14)
−84·4/244·8	−95·8/233·2	−38·6/99·4	−5·7/42·6

– Breast cancer recurrence 0.61 (CI 0.57-0.65)

– Breast cancer mortality 0.70 (CI 0.64-0.75)

Figure 5





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	Number of events (both groups)	O–E	Variance of O–E	Event RR (SE)	p value*
Death with or without recurrence					
Death without recurrence	1117	4·9	258·6	1·02 (0·06)	0·79
Death with recurrence	2694	−224·5	620·2	0·70 (0·03)	<0·00001
Any death	3811	−219·6	878·8	0·78 (0·03)	<0·00001
Death without recurrence (selected groups of causes)					
Vascular disease					
Stroke	64	4·8	15·2	1·37 (0·30)	0·27
Pulmonary embolus†	12	2·5	3·0	2·30 (0·90)	0·25
Heart and other vascular	212	−6·1	50·1	0·89 (0·13)	0·43
Neoplastic disease					
Uterus, excluding cervix‡	10	3·2	2·2	4·28 (1·52)	0·07
Other neoplastic	187	−0·1	44·2	1·00 (0·15)	1·00
Other specified cause	312	4·6	71·0	1·07 (0·12)	0·63
Unspecified cause	320	−4·0	72·9	0·95 (0·11)	0·68
Second cancer incidence without previous recurrence (selected sites)					
Contralateral breast, by age at entry (years)					
<45	110	−17·7	27·2	0·52 (0·14)	0·001
45–54	169	−18·8	41·5	0·64 (0·12)	0·004
55–69	268	−28·7	64·0	0·64 (0·10)	0·0001
≥70	17	0·1	4·1	..	..
All ages	564	−65·1	136·7	0·62 (0·07)	<0·00001
Uterus, excluding cervix‡, by age at entry (years)					
<45	11	0·1	2·7	1·04 (0·62)	1·00
45–54	25	3·3	5·9	1·75 (0·55)	0·25
55–69	71	18·0	16·6	2·96 (0·44)	0·00002
≥70	1	0·8	0·2	..	..
All ages	108	22·2	25·4	2·40 (0·32)	0·00002

Early assessment 10 years vs 5 Tamoxifen

- NSABP B-14
- Scottish trial
- ?

……..conflicting evidence – 5 years became the standard duration for tamoxifen.

-3 endometrial malignacies/1000pts vs 0.76/1000 general population,

- thrombroembolic risk increased

Arrival of aromatase inhibitors –head to head comparison with 5 years of tamoxifen in post-menopausal women

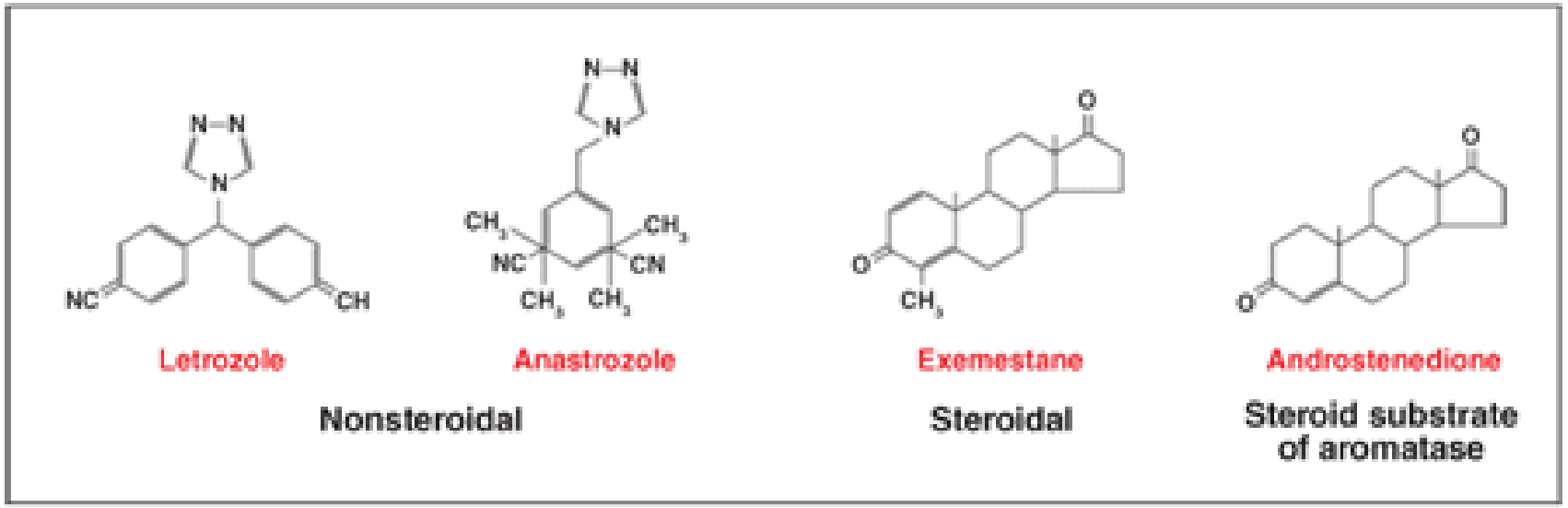


Figure 2: Steroidal and Nonsteroidal Aromatase Inhibitors—Letrozole and anastrozole are nonsteroidal third-generation aromatase inhibitors. The steroidal aromatase inhibitor exemestane is an analog of androstenedione, the androgenic substrate of aromatase.

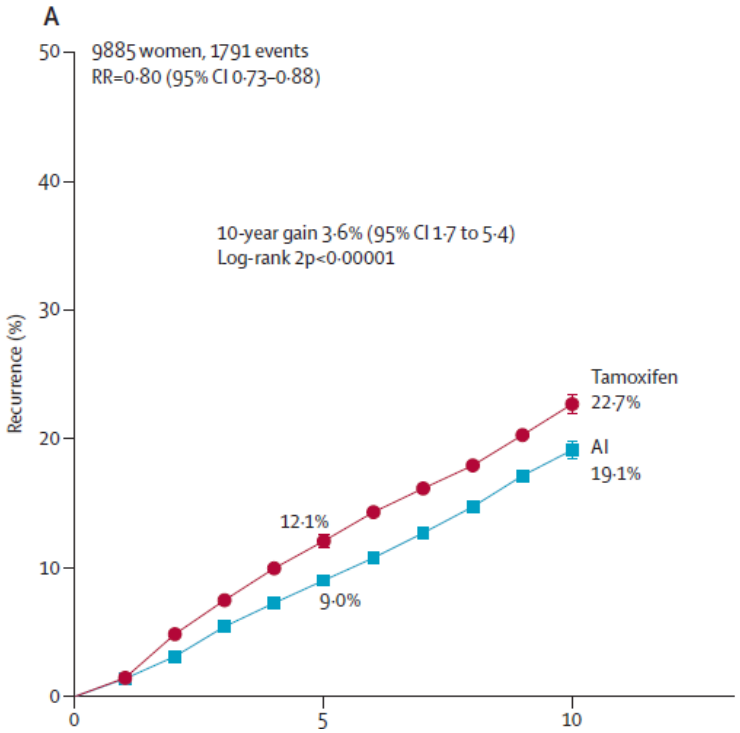
Aromatase inhibitors

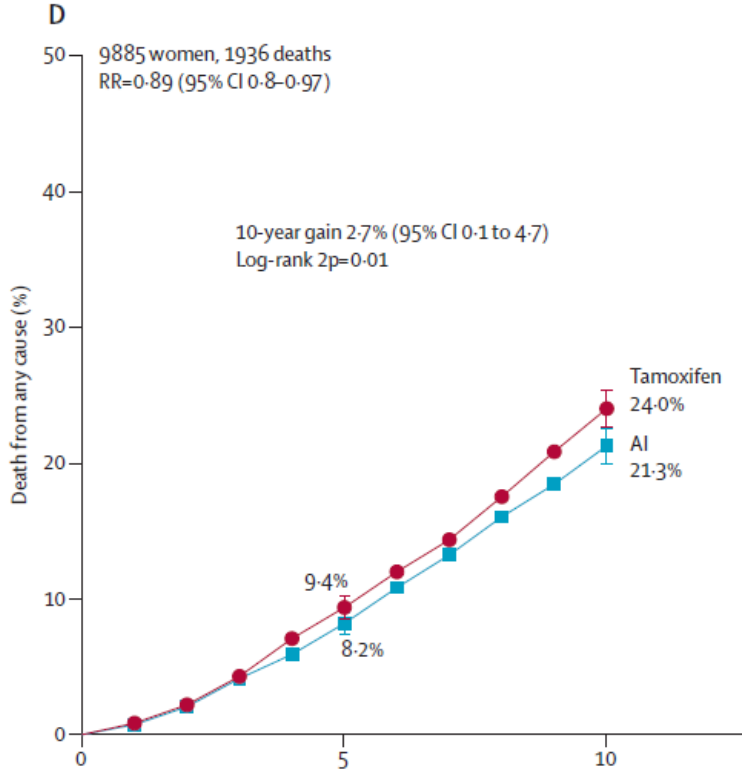
- Reduce breast cancer recurrence and mortality compared to tamoxifen in post-menopausal women
  - Modest but significant benefit
  - Generally more toxic
  - 1st line unless reason not to
  - Some AI is better than none

- EBCTCG Meta-analysis 2015 (Lancet)

Aromatase Inhibitor vs Tamoxifen

– **<u>AI for 5 years vs tamoxifen for 5 years</u>** (n = 9885):
  - Reduction in breast cancer recurrence especially during years 0-1 (RR 0·64, 95% CI 0·52-0·78) and 2-4 (RR 0·80, 0·68-0·93); no further impact on recurrence rates after the 5-year treatment period
  - Reduction in breast cancer mortality at 10 years: (12·1% vs 14·2%; RR 0·85, 0·75-0·96)





Aromatase Inhibitor vs Tamoxifen + Aromatase Inhibitor

- **<u>AI alone versus a short course of tamoxifen (2-3 years) followed by an AI out to 5 years</u>** (n = 12,799).
- Treatment with an AI alone resulted in:
  - Lower recurrence rates during years 0 to 1 (RR 0.74, 95% CI 0.62-0.89).
  - Similar recurrence rates during years 2 to 4, when both groups were treated with an AI (RR 0.99, 95% CI 0.85-1.15)
  - A trend towards reduced breast cancer mortality (RR 0.89, 95% CI 0.78-1.03)

Tamoxifen VS Tamoxifen + Aromatase Inhibitor

- **<u>Tamoxifen alone vs a short course of tamoxifen (2-3 yrs) followed by an AI</u>** (n = 11,798); switch to an AI resulted in:
  - Reduced breast cancer recurrence during years 2 to 4 (RR 0.56, 95% CI 0.46-0.67)
  - Fewer deaths from breast cancer (RR 0.84, 95% CI 0.72-0.96)

Interpretation Aromatase inhibitors reduce recurrence rates by about 30% (proportionately) compared with tamoxifen while treatments differ, but not thereafter. 5 years of an aromatase inhibitor reduces 10-year breast cancer mortality rates by about 15% compared with 5 years of tamoxifen, hence by about 40% (proportionately) compared with no endocrine treatment.

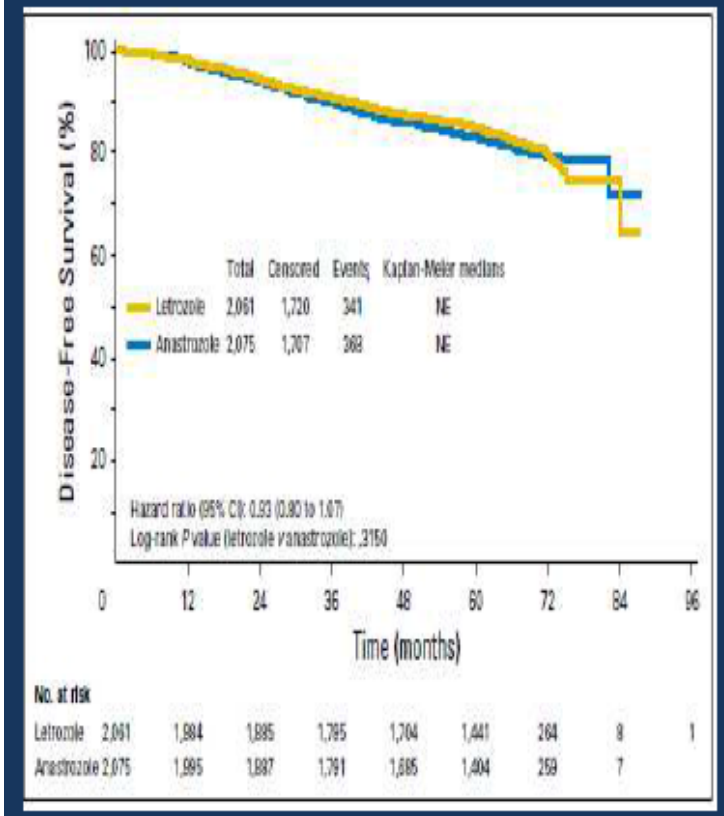
- What about AI + tamoxifen vs AI alone (i.e. the AI first in sequential therapy)

- BIG 1-98
  - 8000 women
  - Tamoxifen 5 yrs vs letrozole 5 yrs vs sequential treatment with 2 yrs of one drug followed by 3 years of the other
  - Tamoxifen monotherapy inferior but no difference in DFS or OS between the sequential therapies and letrozole monotherapy

One of these things is just like the other (probably)…..

FACE Trial

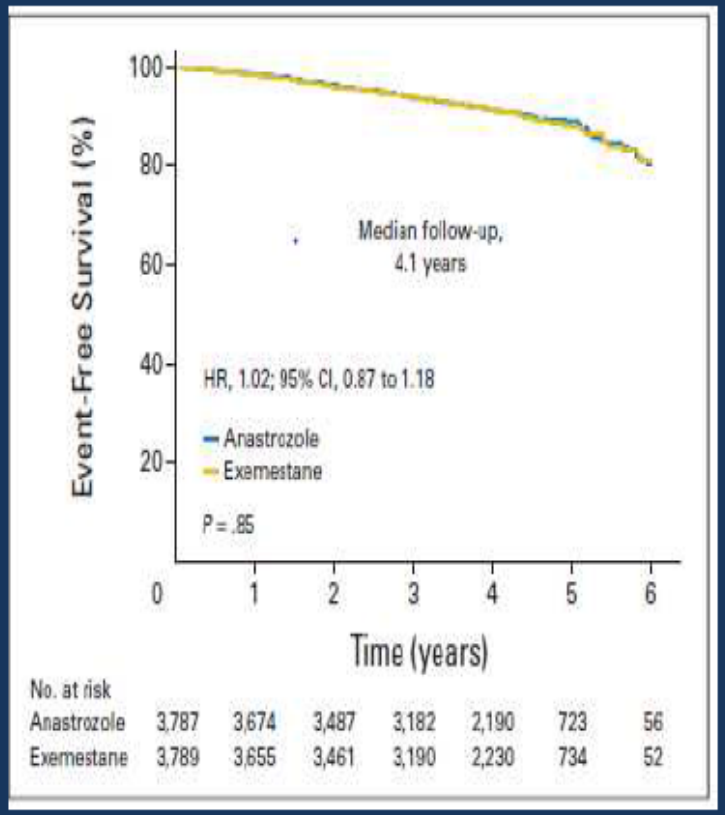
Letrozole vs Anastrozole



Smith et al, J Clin Oncol 2017

MA.27 Trial

Exemestane vs Anastrozole



Goss et al, J Clin Oncol 2013

Aromatase inhibitor toxicity

- Fracture risk

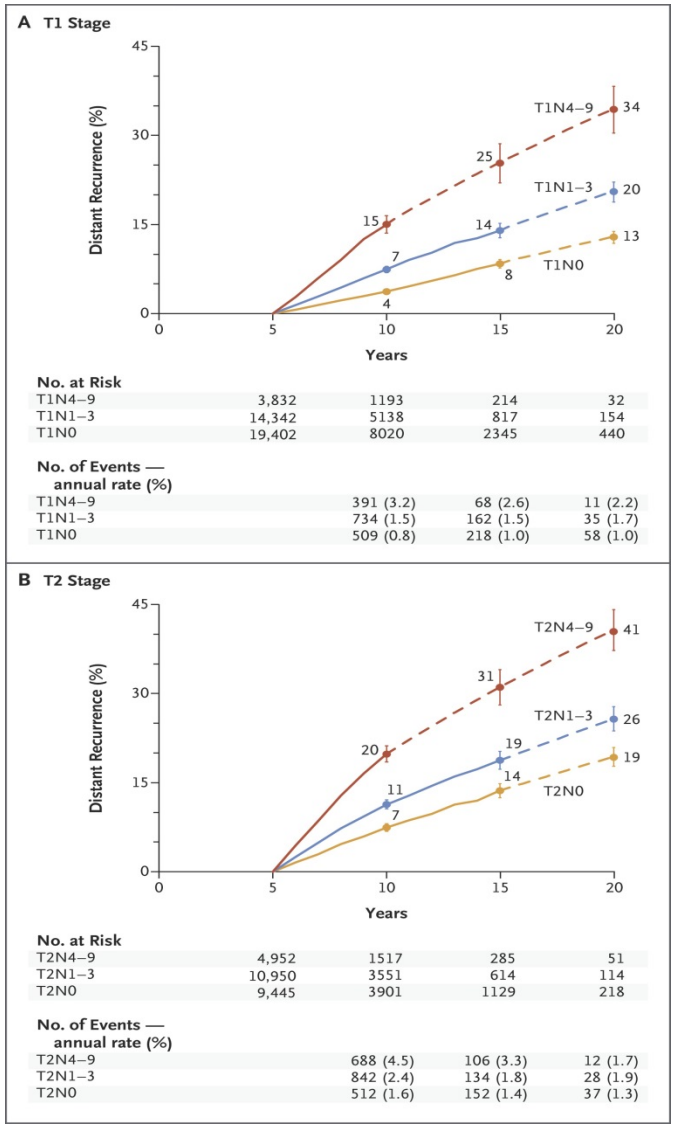
Clinical Study	AI, n (%)	Tamoxifen/ Placebo, n (%)	Increase, %	Reference
ATAC	340 (11.0)	237 (7.7)	43	Howell et al 2005
BIG 1-98	228 (5.8)	162 (4.1)	41	Thurlimann et al 2005
IES	162 (7.0)	111 (4.9)	45	Coombes et al 2006
ABCSG/ ARNO	34 (2.0)	16 (1.0)	113	Jakesz et al 2005
MA.17	137 (5.3)	119 (4.6)	15	Perez et al 2006

	Number of patients (%)		Odds ratio, anastrozole vs tamoxifen (95% CI)	p
	Anastrozole (n=3092)	Tamoxifen (n=3094)		
Hot flushes	1104 (35·7%)	1264 (40·9%)	0·80 (0·73–0·89)	<0·0001
Nausea and vomiting	393 (12·7%)	384 (12·4%)	1·03 (0·88–1·19)	0·7
Fatigue/tiredness	575 (18·6%)	544 (17·6%)	1·07 (0·94–1·22)	0·3
Mood disturbances	597 (19·3%)	554 (17·9%)	1·10 (0·97–1·25)	0·2
Arthralgia	1100 (35·6%)	911 (29·4%)	1·32 (1·19–1·47)	<0·0001*
Vaginal bleeding	167 (5·4%)	317 (10·2%)	0·50 (0·41–0·61)	<0·0001
Vaginal discharge	109 (3·5%)	408 (13·2%)	0·24 (0·19–0·30)	<0·0001
Endometrial cancer†	5 (0·2%)	17 (0·8%)	0·29 (0·11–0·80)	0·02
Fractures‡	340 (11·0%)	237 (7·7%)	1·49 (1·25–1·77)	<0·0001*
Hip	37 (1·2%)	31 (1·0%)	1·20 (0·74–1·93)	0·5
Spine	45 (1·5%)	27 (0·9%)	1·68 (1·04–2·71)	0·03*
Wrist/Colles	72 (2·3%)	63 (2·0%)	1·15 (0·81–1·61)	0·4
All other sites§	220 (7·1%)	142 (4·6%)	1·59 (1·28–1·98)	<0·0001*
Ischaemic cardio-vascular disease	127 (4·1%)	104 (3·4%)	1·23 (0·95–1·60)	0·1
Ischaemic cerebro-vascular events	62 (2·0%)	88 (2·8%)	0·70 (0·50–0·97)	0·03
Venous thrombo-embolic events	87 (2·8%)	140 (4·5%)	0·61 (0·47–0·80)	0·0004
Deep venous thrombo-embolic events	48 (1·6%)	74 (2·4%)	0·64 (0·45–0·93)	0·02
Cataracts	182 (5·9%)	213 (6·9%)	0·85 (0·69–1·04)	0·1

*In favour of tamoxifen. †n=2229 for anastrozole, 2236 for tamoxifen, excluding patients with hysterectomy at baseline, recorded at any time. ‡Patients with one or more fractures occurring at any time before recurrence (includes patients no longer receiving treatment). §Patients may have had one or more fractures at different sites.

Table: **Prespecified adverse events on treatment or within 14 days of discontinuation**

Beyond 5 years- can we do better



EBCCTG – 20 year follow up for patients treated with 5 years of endocrine therapy –T1No patients at 20 years have cumulative risk of 13% for distant recurrence

Extended therapy warranted?
Is it effective?
For all endocrine sensitive patients?
Cumulative toxicities?
Overall quality of life and compliance?
Cost?

Difficulties with extended treatment trials

- Choice of endpoint – death through noncancer causes common esp in post menopausal breast cancer trials (DDFS?)
- Competing with carryover effect of tamoxifen where control arm uses 5 years of the drug – trials may need extended follow up
- Assessment of compliance