OPTIMAL LENGTH OF HORMONE THERAPY FOR EARLY-STAGE HORMONE RECEPTOR POSITIVE BREAST CANCER

WADE SMITH, MD

Assistant Clinical Professor
Department of Medical Oncology & Therapeutic Research
City of Hope Orange County

Disclosures

- Consultant for Biotheranostics and Novartis.

OPTIMAL LENTGH OF HORMONE THERAPY FOR EARLY-STAGE HORMONE RECEPTOR POSITIVE BREAST CANCER

- Premenopausal Patients
  - Tamoxifen Therapy
  - Combined Endocrine Therapy
  - Extended Endocrine Therapy
- Postmenopausal Patients
  - Aromatase Inhibitor Therapy
  - Tamoxifen Therapy
  - Extended Endocrine Therapy

Tamoxifen – Toxicity Considerations

Venous thromboembolism

Uterine cancer

Eye problems (cataracts / macular edema)

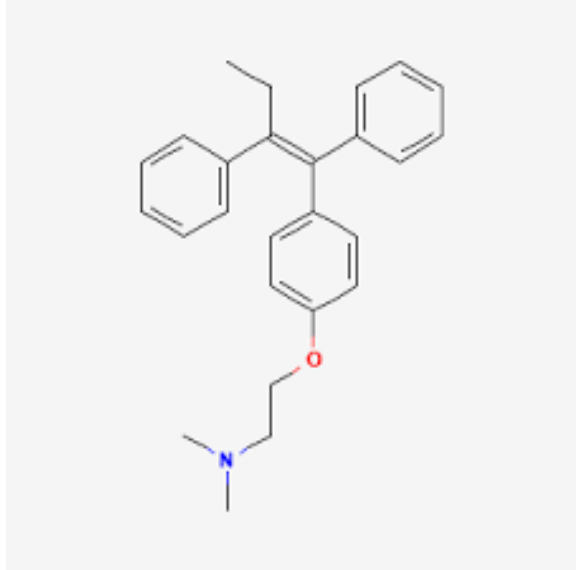
Fatty liver disease

Sexual dysfunction

Hot flashes

Bone health

Alopecia / dermatologic



Aromatase Inhibitors – Toxicity Considerations

Musculoskeletal side effects

Bone health

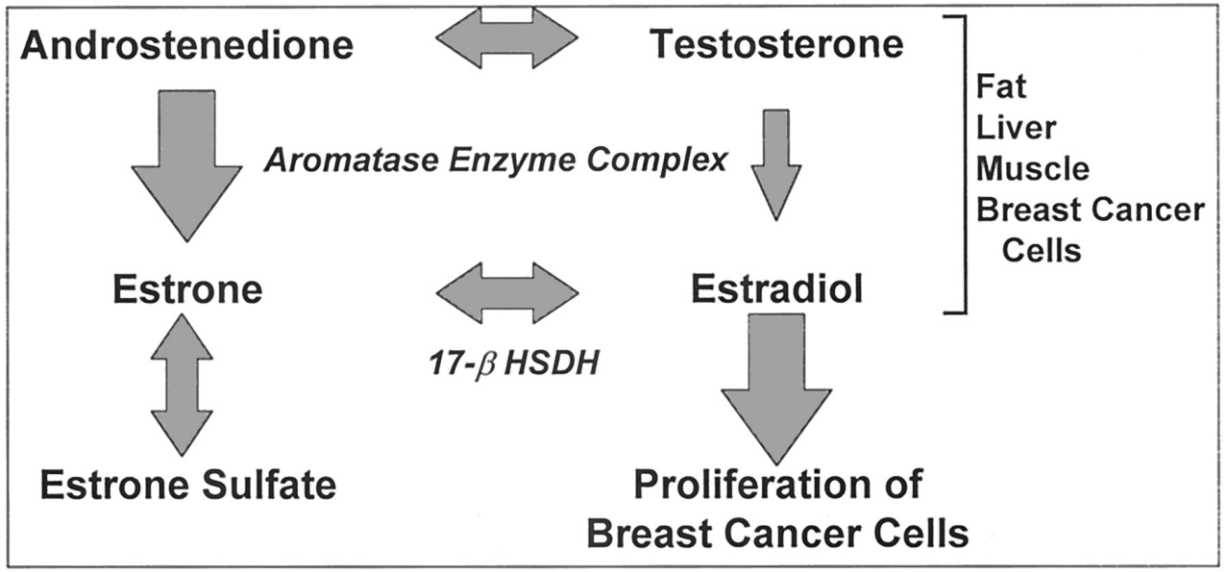
Hyperlipidemia

Cardiovascular disease

Cognitive impairment

Ovarian reactivation in premenopausal women

Alopecia / dermatologic



Buzdar et al. CCR, September 2001

Volume 7, Issue 9

Adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer

- Aromatase inhibitor (preferred) versus Tamoxifen as single agent therapy.
- AIs are associated with improved outcomes compared with tamoxifen.
- Some women may better tolerate the toxicities of tamoxifen over an AI.
- Switching between therapies for reasons of side effects / complication is reasonable.
- Important to remember:
  - On tamoxifen – annual pelvic exam (no history of hysterectomy)
  - On AI – bone density monitoring
  - Healthy lifestyle – well-rounded diet, limit etoh intake, maintain healthy body weight (BMI 20-25)
  - Monitor for compliance

Adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer

- Whether treating with tamoxifen alone, aromatase inhibitor alone, or both in sequence, a minimum of 5 years total duration is recommended.
- With higher-risk disease, extended endocrine treatment may be considered (ie. a total duration between 7 and 10 years).
- With low-risk disease, extended endocrine therapy with a goal of decreasing the likelihood of new breast cancers or recurrences may be considered.
- With extended endocrine therapy – toxicity-related risk persists throughout the entirety of therapy.

Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer

- High-risk breast cancer, we suggest ovarian function suppression (OFS) plus an aromatase inhibitor (AI) or tamoxifen, rather than tamoxifen alone
    - Large tumor size
    - Pathologically-involved axillary lymph nodes
    - High risk of recurrence based on a genomic assay
    - Young age
- Low-risk breast cancer, tamoxifen as single-agent therapy preferred ovarian suppression plus endocrine therapy.
    - Older than 35 years who are without indications for chemotherapy

Adjuvant ovarian suppression in premenopausal breast cancer (SOFT Trial)

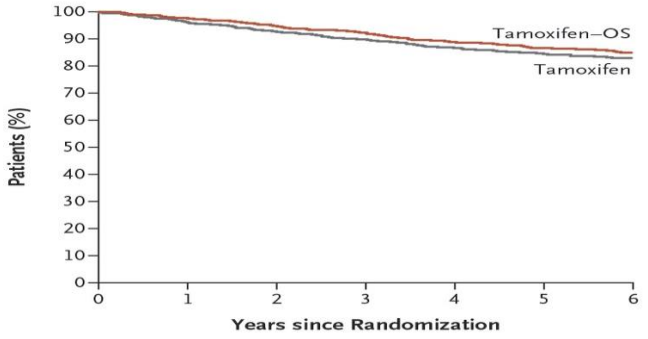
Francis PA et al. N Engl J Med. 2015;372(5):436

Adding ovarian suppression to tamoxifen did not provide a significant benefit in the overall study population.

Patients at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, the addition of ovarian suppression improved disease outcomes.

Further improvement was seen with the use of exemestane plus ovarian suppression.

A Disease-free Survival



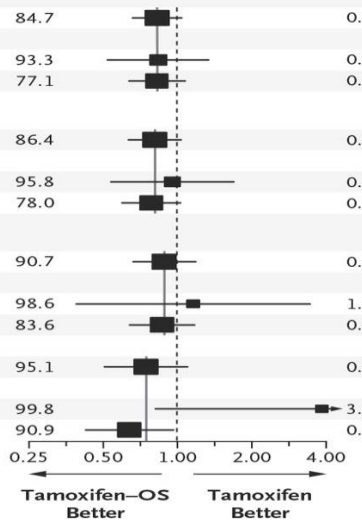
No. at Risk							
Tamoxifen	1018	951	895	847	719	525	309
Tamoxifen–OS	1015	966	927	878	742	556	349

	No. of Patients	No. of Patients with Event	5-Yr Rate %
Tamoxifen	1018	160	84.7
Tamoxifen–OS	1015	139	86.6

Hazard ratio for recurrence, second invasive cancer, or death, 0.83 (95% CI, 0.66–1.04)
P=0.10

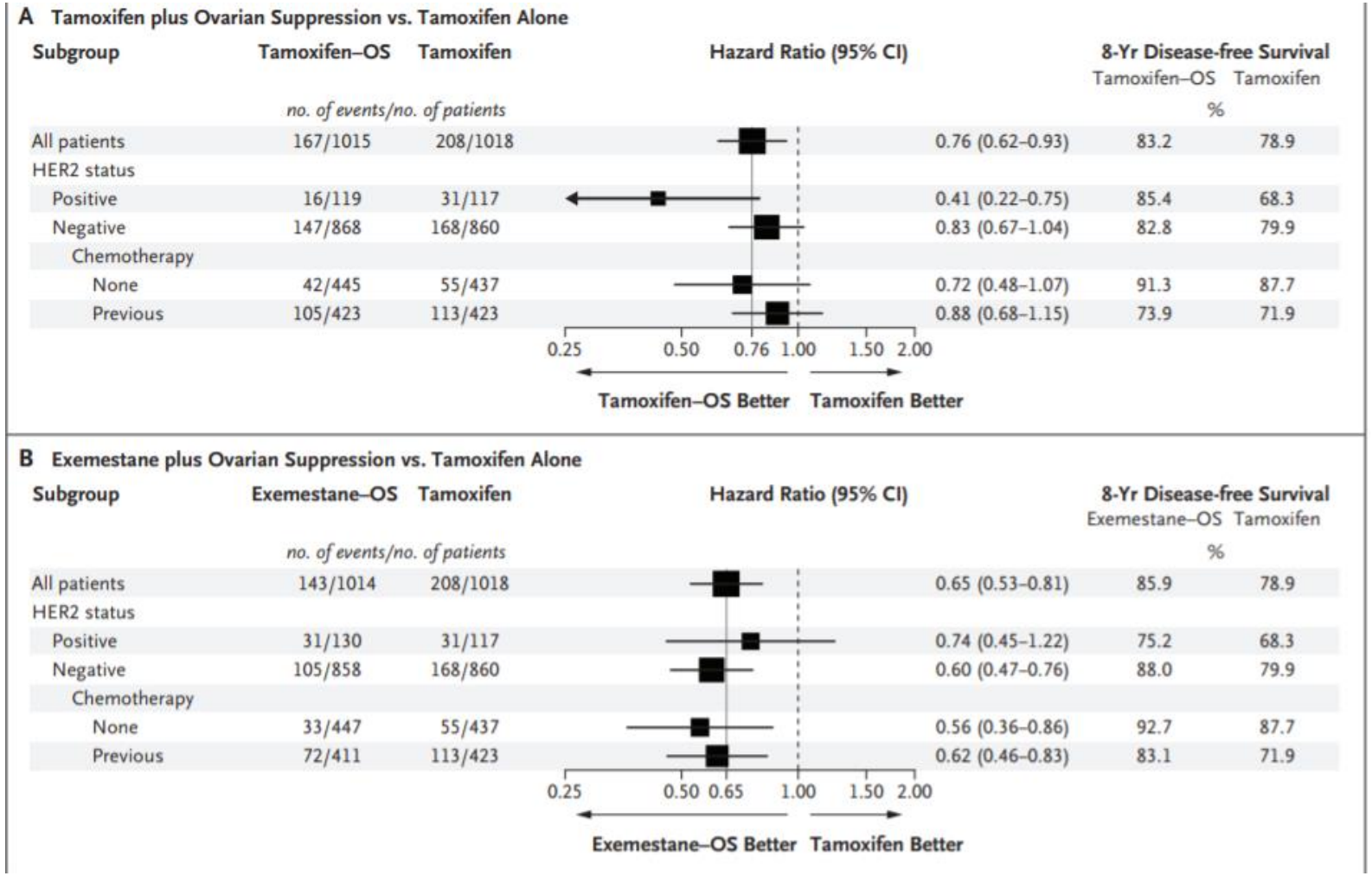
B End Points, Overall and According to Chemotherapy Cohort

End Point	No. of Patients		No. of Patients with Event		5-Yr Rate (%)		Hazard Ratio (95% CI)	P Value
	Tamoxifen–OS	Tamoxifen	Tamoxifen–OS	Tamoxifen	Tamoxifen–OS	Tamoxifen		
Disease-free survival								
All patients	1015	1018	139	160	86.6	84.7	0.83 (0.66–1.04)	0.10
Prior chemotherapy								
No	473	476	32	38	93.4	93.3	0.83 (0.52–1.34)	0.96
Yes	542	542	107	122	80.7	77.1	0.82 (0.64–1.07)	
Freedom from breast cancer								
All patients	1015	1018	120	140	88.4	86.4	0.81 (0.63–1.03)	0.09
Prior chemotherapy								
No	473	476	23	24	95.1	95.8	0.95 (0.54–1.69)	0.54
Yes	542	542	97	116	82.5	78.0	0.78 (0.60–1.02)	
Freedom from distant recurrence								
All patients	1015	1018	89	96	91.3	90.7	0.88 (0.66–1.18)	0.40
Prior chemotherapy								
No	473	476	7	6	98.7	98.6	1.16 (0.39–3.44)	0.62
Yes	542	542	82	90	84.8	83.6	0.87 (0.64–1.17)	
Overall survival								
All patients	1015	1018	47	59	96.7	95.1	0.74 (0.51–1.09)	0.13
Prior chemotherapy								
No	473	476	8	2	99.2	99.8	3.84 (0.81–18.08)	0.03
Yes	542	542	39	57	94.5	90.9	0.64 (0.42–0.96)	



Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer (SOFT Trial).

Francis PA et al. N Engl J Med. 2018;379(2):122.



A Tamoxifen plus Ovarian Suppression vs. Tamoxifen Alone

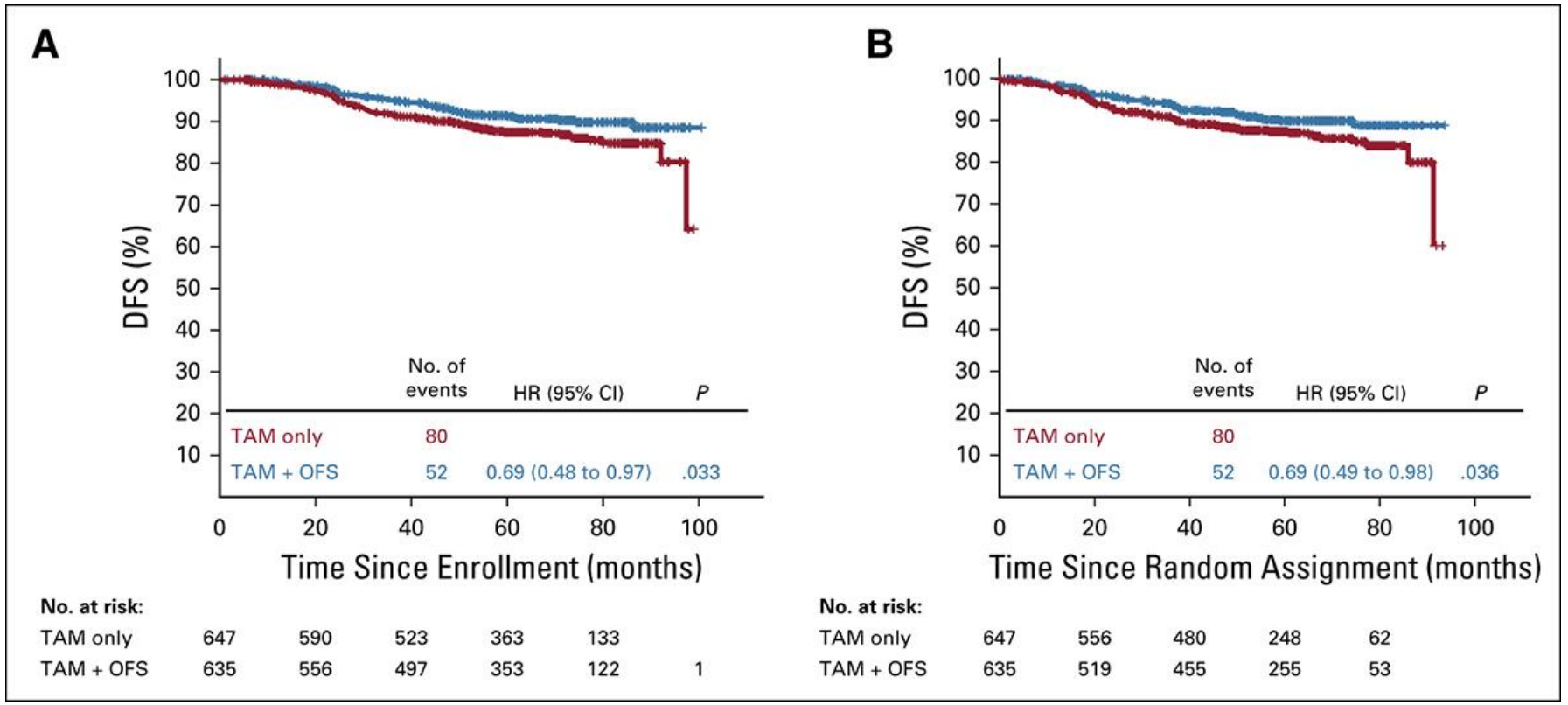
Subgroup	Tamoxifen–OS	Tamoxifen	Hazard Ratio (95% CI)	8-Yr Disease-free Survival Tamoxifen–OS	8-Yr Disease-free Survival Tamoxifen
	no. of events/no. of patients			%	
All patients	167/1015	208/1018	0.76 (0.62–0.93)	83.2	78.9
HER2 status					
Positive	16/119	31/117	0.41 (0.22–0.75)	85.4	68.3
Negative	147/868	168/860	0.83 (0.67–1.04)	82.8	79.9
Chemotherapy					
None	42/445	55/437	0.72 (0.48–1.07)	91.3	87.7
Previous	105/423	113/423	0.88 (0.68–1.15)	73.9	71.9

B Exemestane plus Ovarian Suppression vs. Tamoxifen Alone

Subgroup	Exemestane–OS	Tamoxifen	Hazard Ratio (95% CI)	8-Yr Disease-free Survival Exemestane–OS	8-Yr Disease-free Survival Tamoxifen
	no. of events/no. of patients			%	
All patients	143/1014	208/1018	0.65 (0.53–0.81)	85.9	78.9
HER2 status					
Positive	31/130	31/117	0.74 (0.45–1.22)	75.2	68.3
Negative	105/858	168/860	0.60 (0.47–0.76)	88.0	79.9
Chemotherapy					
None	33/447	55/437	0.56 (0.36–0.86)	92.7	87.7
Previous	72/411	113/423	0.62 (0.46–0.83)	83.1	71.9

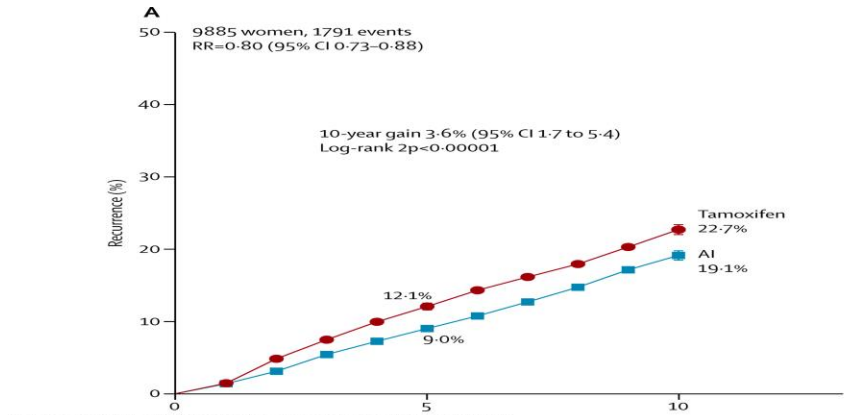
Premenopausal women with high-risk hormone receptor-positive breast cancer: 2 years of OFS plus tamoxifen.

Adding Ovarian Suppression to Tamoxifen for Premenopausal Breast Cancer: A Randomized Phase III Trial (Kim HA et al. J Clin Oncol, February 10, 2020, Volume 38 (5), p 434–443.



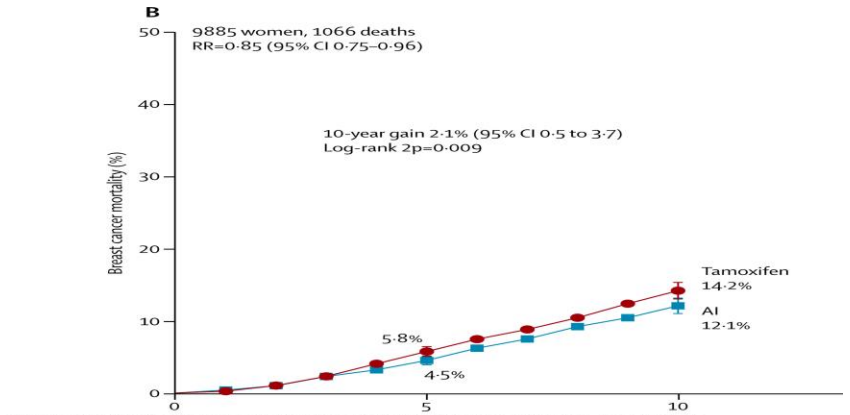
Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomized trials.

EBCTCG Lancet. 2015;386(10001):1341



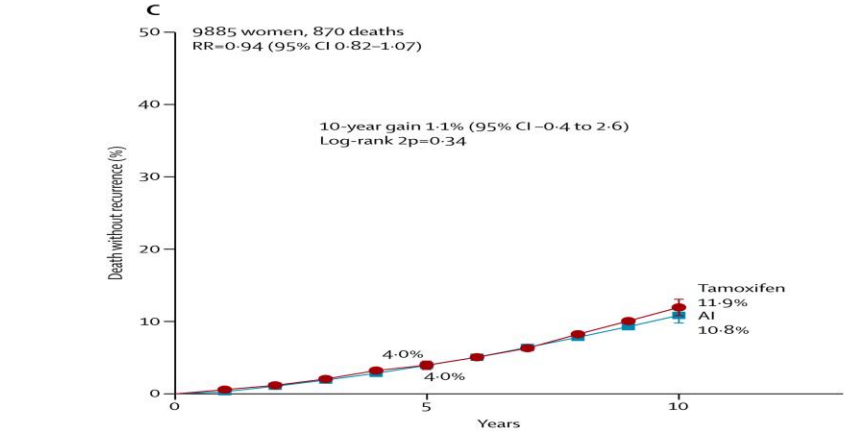
Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·62 (157/9691)	2·14 (285/13 336)	2·33 (365/15 648)	3·23 (20/619)
Tamoxifen	2·41 (230/9542)	2·62 (338/12 906)	2·48 (372/14 985)	4·54 (24/529)
Rate ratio (95% CI)	0·64 (0·52–0·78)	0·80 (0·68–0·93)	0·92 (0·79–1·06)	0·72 (0·39–1·30)
from (O–E)/V	−41·1/92·8	−34·1/149·0	−15·5/177·2	−3·6/10·7



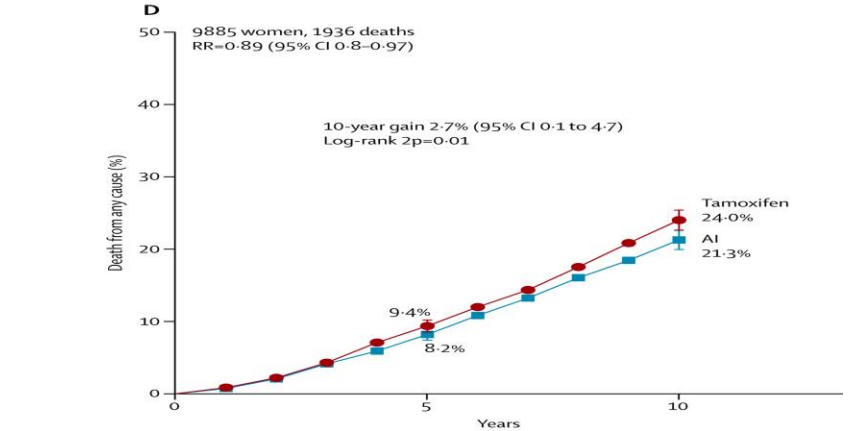
Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	0·52 (0·39–0·66)	1·23 (1·05–1·41)	1·66 (1·46–1·86)	1·93 (0·88–2·99)
Tamoxifen	0·51 (0·39–0·67)	1·60 (1·38–1·83)	1·81 (1·60–2·02)	1·88 (0·77–2·99)
Rate ratio (95% CI)	0·98 (0·66–1·46)	0·74 (0·60–0·91)	0·90 (0·76–1·07)	1·01 (0·45–2·33)
from (O–E)/V	−0·4/24·3	−27·2/90·7	−13·6/129·4	0·1/5·6



Death-without-recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	0·54 (52/9691)	0·99 (132/13 336)	1·46 (229/15 648)	3·07 (19/619)
Tamoxifen	0·60 (57/9542)	0·95 (122/12 906)	1·63 (244/14 985)	2·84 (15/529)
Rate ratio (95% CI)	0·89 (0·61–1·30)	1·03 (0·81–1·32)	0·88 (0·73–1·05)	1·28 (0·64–2·56)
from (O–E)/V	−3·2/27·0	2·0/62·5	−14·9/114·4	2·0/8·1



Death rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·05 (103/9775)	2·18 (301/13 777)	3·06 (500/16 333)	4·76 (32/672)
Tamoxifen	1·10 (106/9661)	2·50 (338/13 506)	3·35 (530/15 805)	4·44 (26/586)
Rate ratio (95% CI)	0·93 (0·71–1·23)	0·85 (0·72–0·99)	0·89 (0·79–1·01)	1·16 (0·69–1·99)
from (O–E)/V	−3·6/51·3	−25·2/153·2	−28·4/243·9	2·1/13·6

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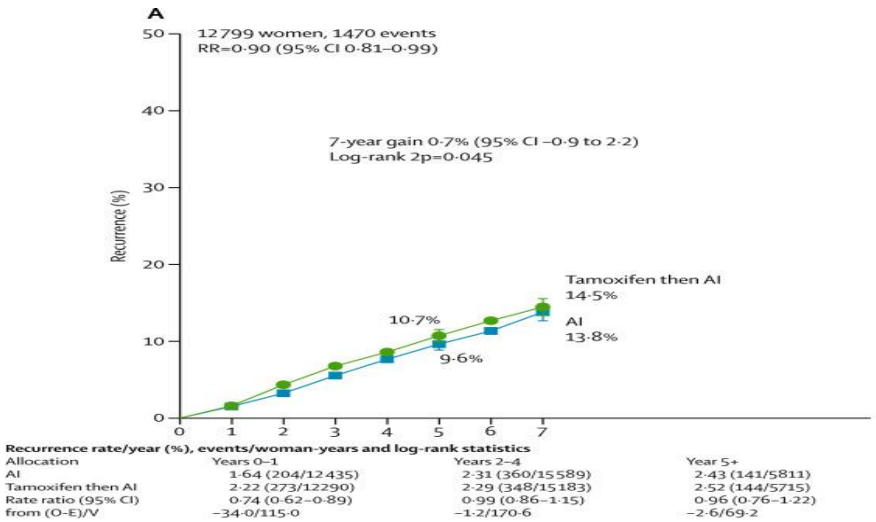
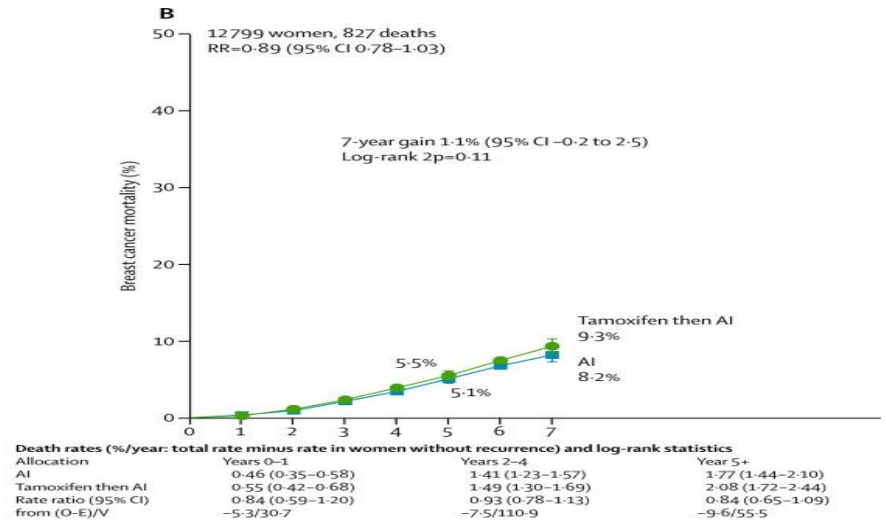


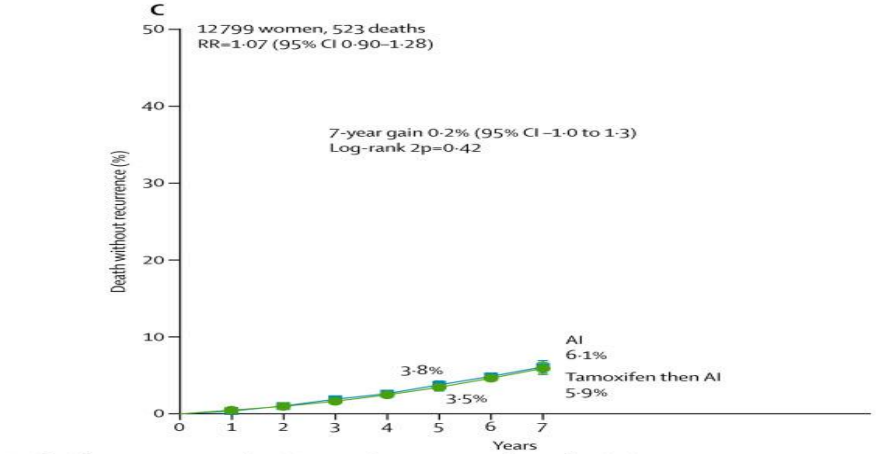
Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	1·64 (204/12 435)	2·31 (360/15 589)	2·43 (141/5811)
Tamoxifen then AI	2·22 (273/12 290)	2·29 (348/15 183)	2·52 (144/5715)
Rate ratio (95% CI)	0·74 (0·62–0·89)	0·99 (0·86–1·15)	0·96 (0·76–1·22)
from (O-E)/V	−34·0/115·0	−1·2/170·6	−2·6/69·2



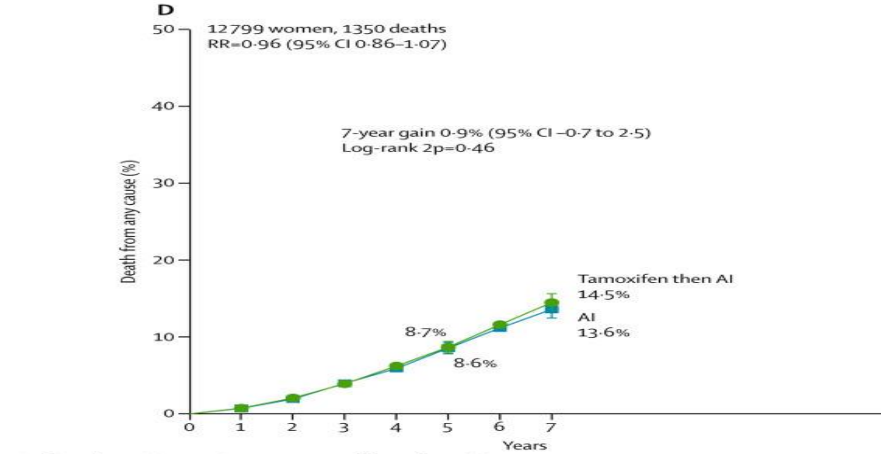
Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	0·46 (0·35–0·58)	1·41 (1·23–1·57)	1·77 (1·44–2·10)
Tamoxifen then AI	0·55 (0·42–0·68)	1·49 (1·30–1·69)	2·08 (1·72–2·44)
Rate ratio (95% CI)	0·84 (0·59–1·20)	0·93 (0·78–1·13)	0·84 (0·65–1·09)
from (O-E)/V	−5·3/30·7	−7·5/110·9	−9·6/55·5



Death-without-recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	0·52 (65/12 435)	0·94 (146/15 589)	1·14 (66/5811)
Tamoxifen then AI	0·50 (61/12 290)	0·82 (124/15 183)	1·07 (61/5715)
Rate ratio (95% CI)	1·04 (0·73–1·48)	1·11 (0·88–1·42)	1·02 (0·72–1·46)
from (O-E)/V	1·2/31·1	7·1/66·2	0·8/30·8



Death rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	0·98 (123/12 576)	2·31 (374/16 200)	2·84 (175/6152)
Tamoxifen then AI	1·04 (130/12 463)	2·27 (361/15 885)	3·08 (187/6064)
Rate ratio (95% CI)	0·94 (0·73–1·20)	1·00 (0·86–1·16)	0·90 (0·73–1·12)
from (O-E)/V	−4·1/61·8	−0·4/177·1	−8·8/86·3

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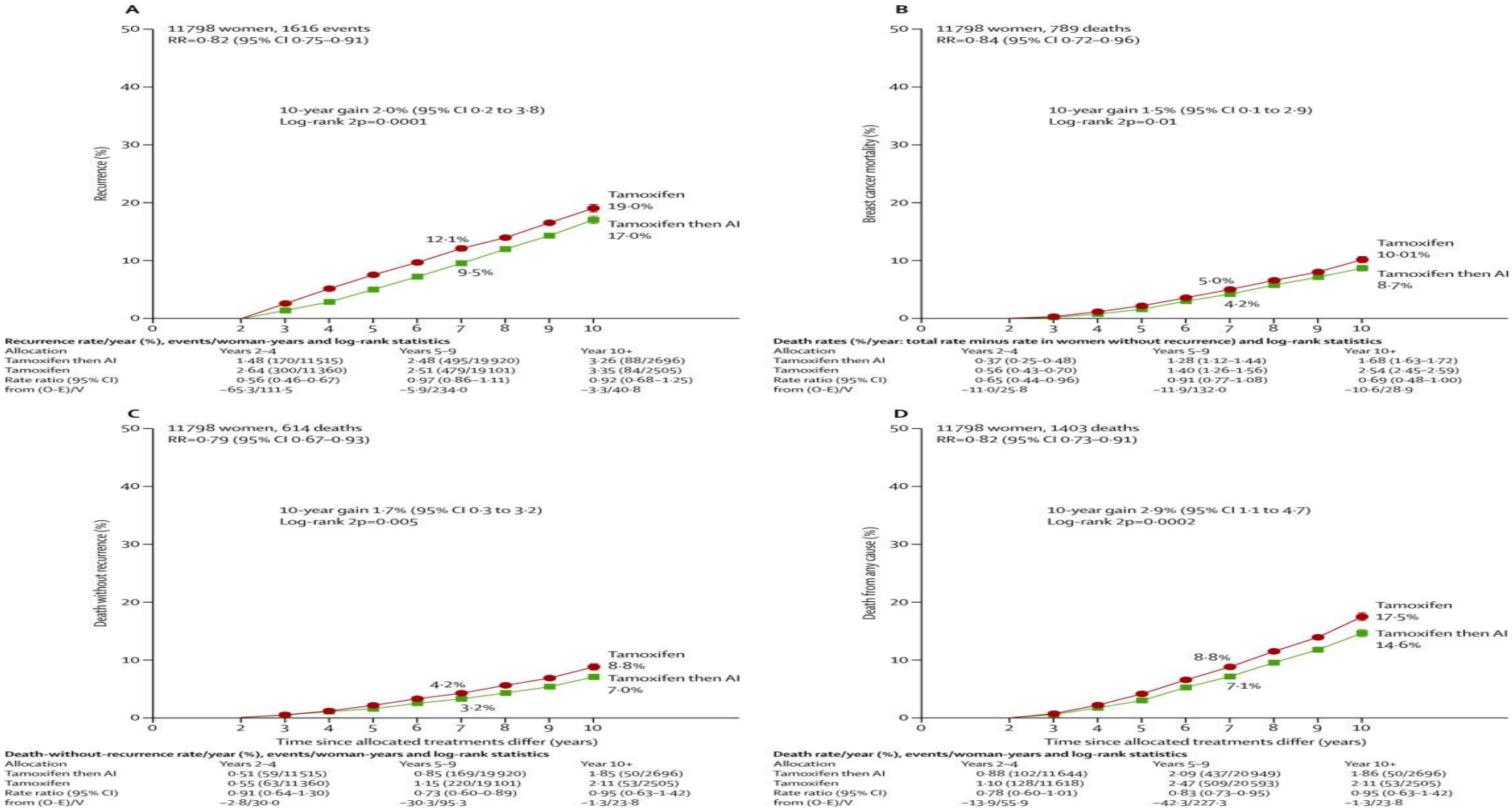


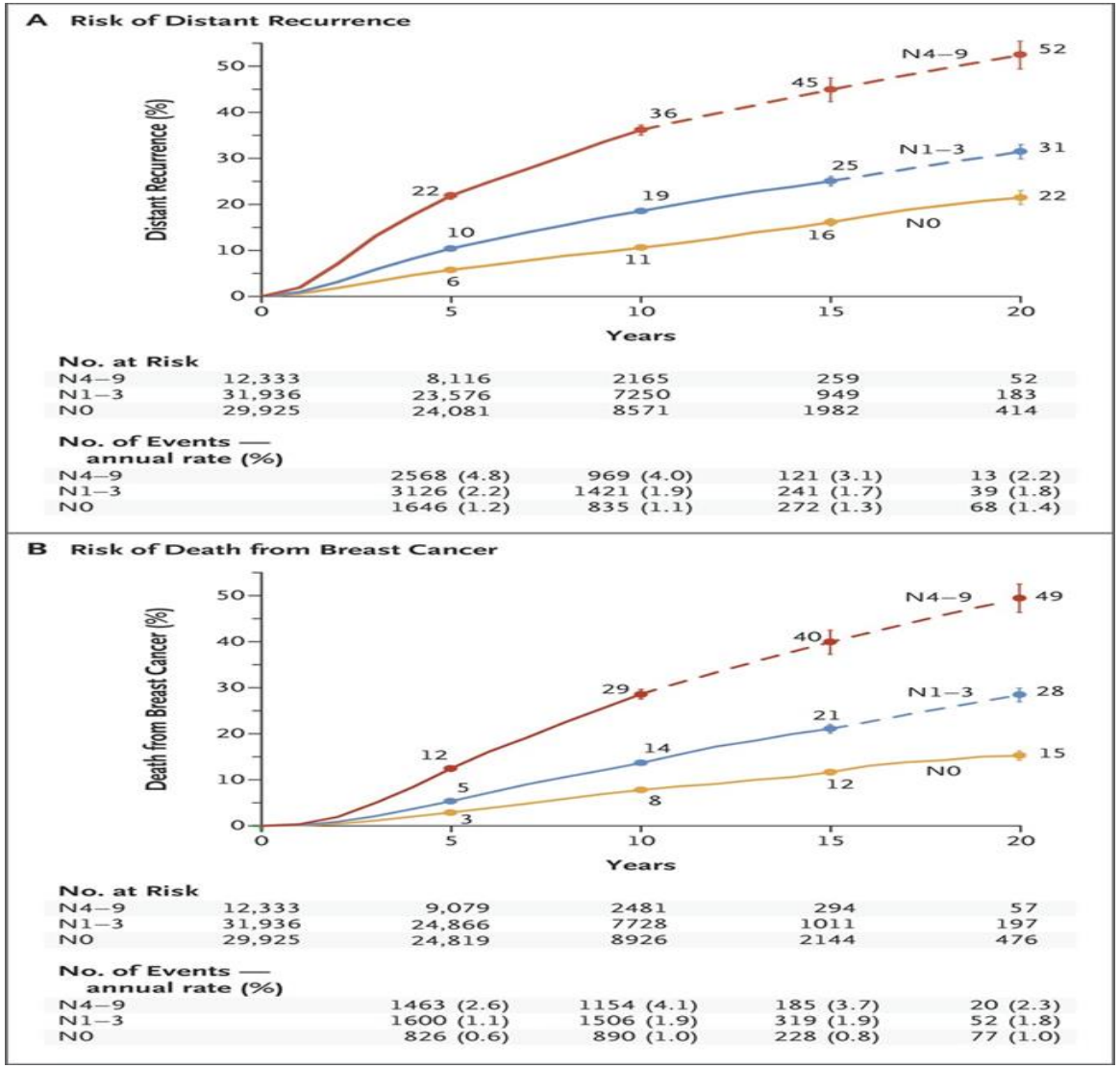
20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years

Pan et al. N Engl J Med. 2017;377(19):1836

- Breast-cancer recurrences occurred at a steady rate throughout the study period from 5 to 20 years.
- Many positive nodes, annual risk of distant recurrence of nearly 3 percent per year.
- One to three positive nodes, annual risk was approximately 2 percent.
- No nodes but T2 or greater lesions, annual risk was approximately 1 percent per year.
- Node-negative and smaller tumors experienced an annual risk of approximately 0.5 to 1.0 percent.

20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years

Pan et al. N Engl J Med. 2017;377(19):1836

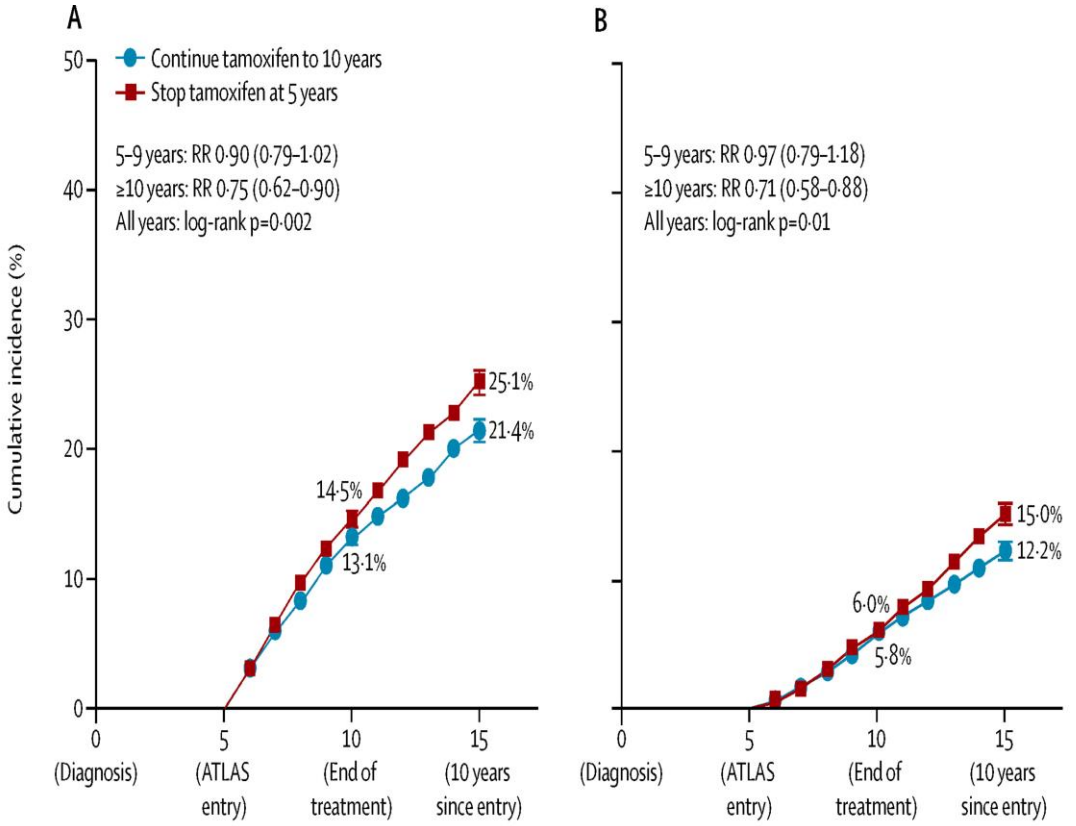


How to select a postmenopausal patient for extended endocrine therapy…

- A valid option for all patients with a prior history of invasive, ER-positive breast cancer.
- Women with larger tumors or node-positive disease.
- Incorporate the risk of both ongoing symptomatic side effects as well as complications (thrombosis, uterine cancer, fracturs, etc.).
- Understand limited role of genomic assays.

Postmenopausal women treated with 5 years of tamoxifen…

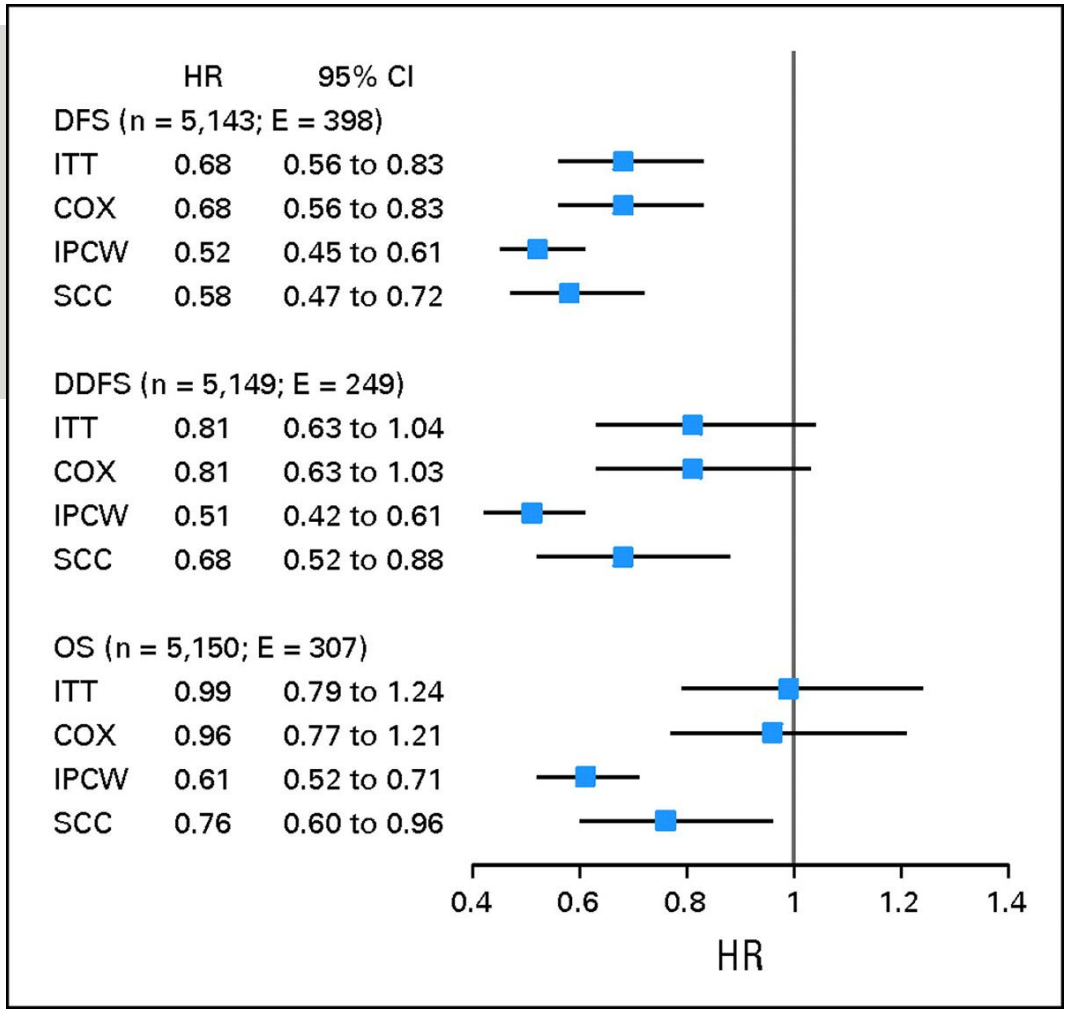
- ATLAS Trial
  - Davies C, et al. Lancet. 2013;381(9869):805.
- Accrued ~7000 women (90 percent of whom were postmenopausal)
- 10 vs 5 years tamoxifen resulted in:
  - Reduced risk of recurrence
  - Reduced breast cancer mortality
  - Decrease in contralateral breast cancer
- aTTom trial also demonstrated decreased RR and breast mortality with 10 vs 5 years tamoxifen.
  - Gray RG et al. J Clin Oncol. 2013;31S:ASCO #5.



	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

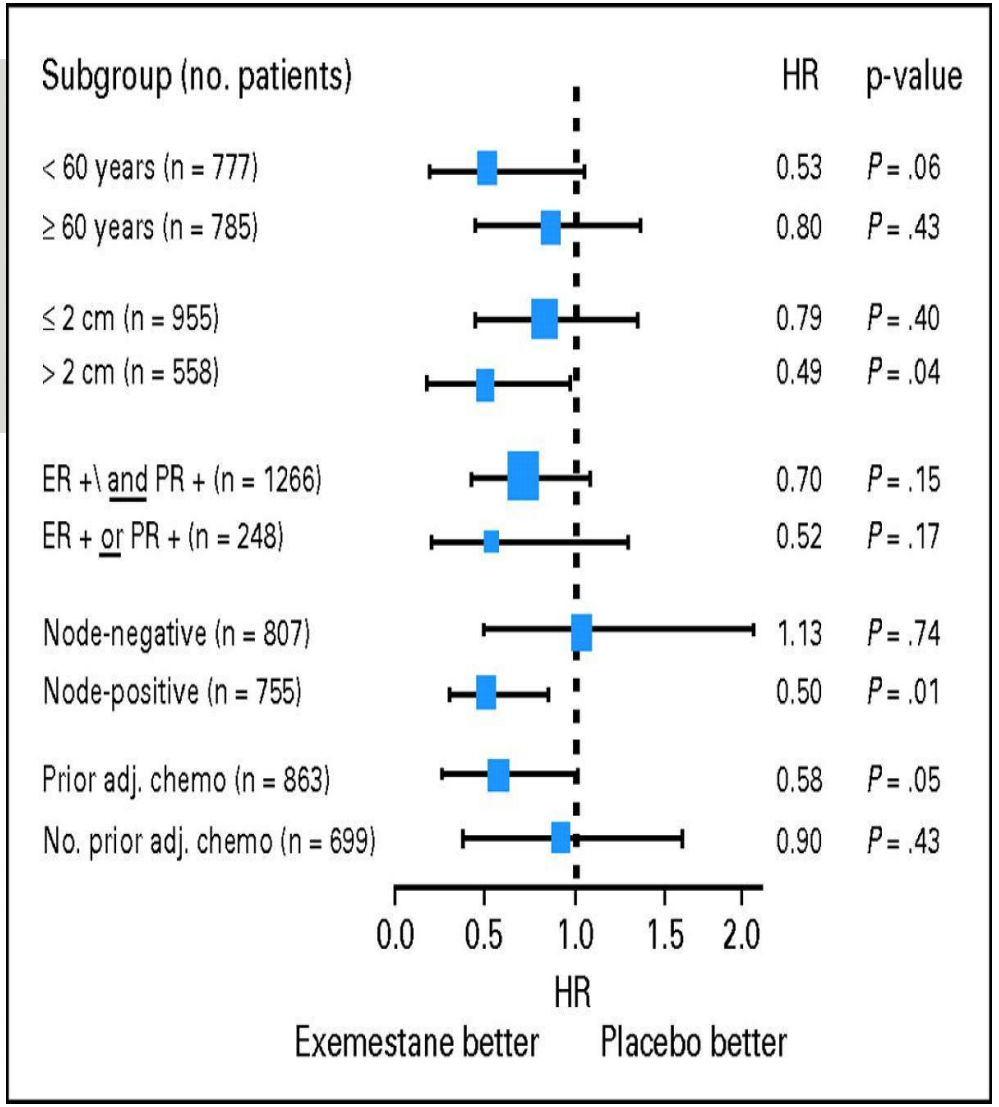
Postmenopausal women treated with 5 years of tamoxifen…

- Followed by 5 years of AI vs placebo:
  - MA.17 trial
  - ~5000 postmenopausal patients
  - 5-year course of letrozole or placebo.
  - Letrozole showed improvement in DFS compared with placebo (hazard ratio [HR] 0.52, 95% CI 0.45-0.61) and an improvement in OS (HR 0.61, 95% CI 0.52-0.71).
    - Jin H et al. J Clin Oncol. 2012;30(7):718. Epub 2011 Oct 31



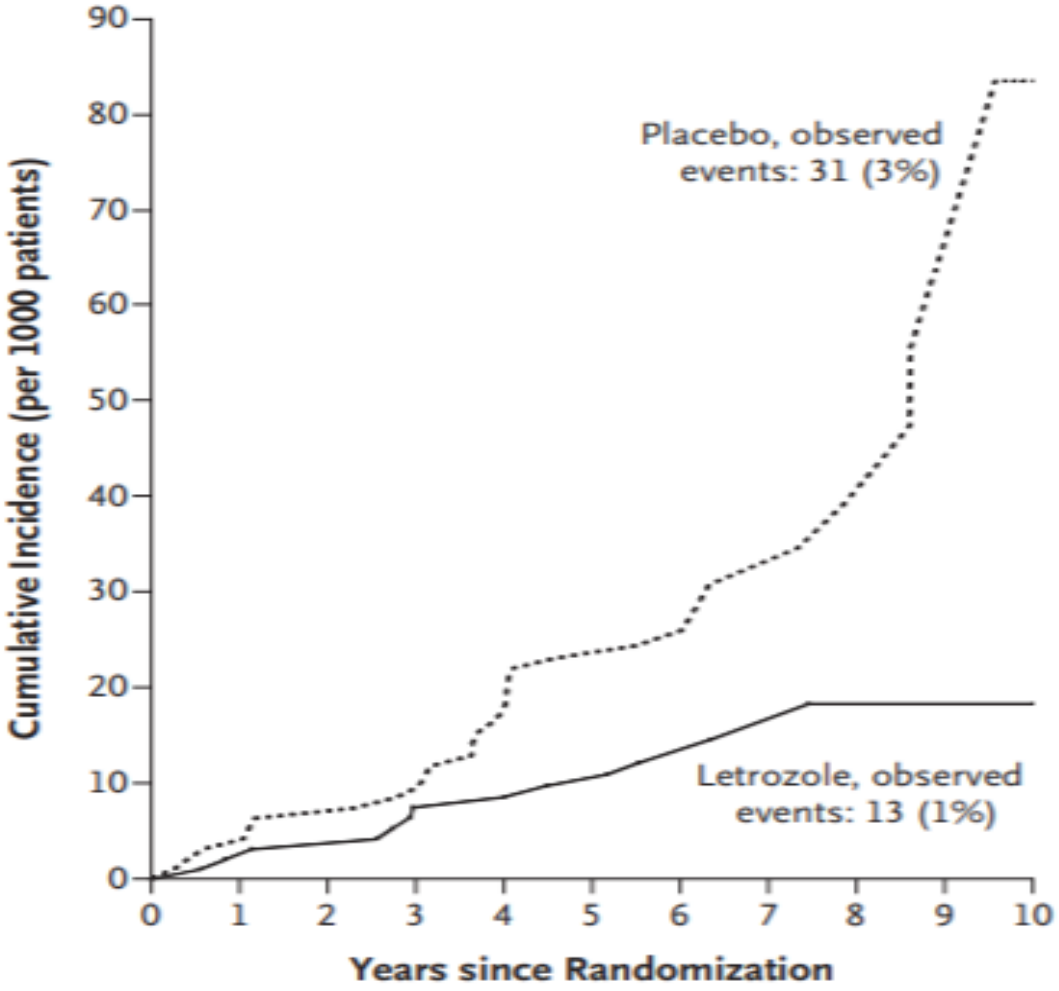
Postmenopausal women treated with 5 years of tamoxifen…

- Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial.
    - Mamounas EP et al, J Clin Oncol. 2008;26(12):1965
- Exemestane x 5 years resulted in non-statistically significant improvement in DFS and statistically significant improvement in RFS.



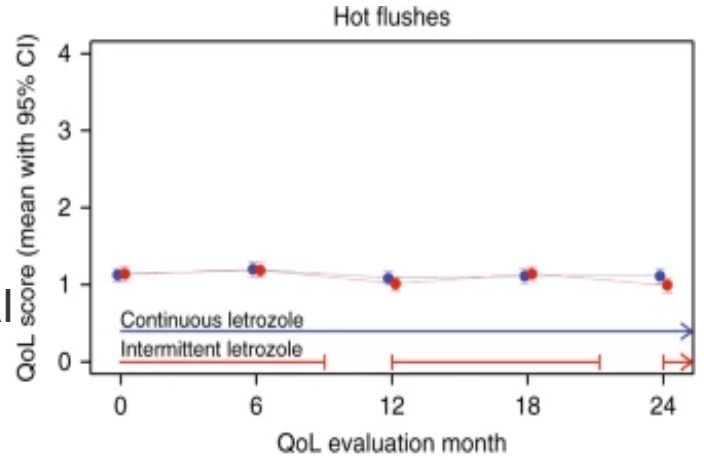
Postmenopausal women treated with 5 years of aromatase inhibitor…

- MA.17R trial
  - Goss PE et al. N Engl J Med. 2016;375(3):209.
- 1900 postmenopausal women.
- Following five years of letrozole (and any duration of tamoxifen), an additional 5 years of letrozole vs placebo improved 5-yr DFS but not OS. (95 percent [95% CI 93-96 percent] versus 91 percent [95% CI 89-93 percent]).
- Nearly one-half of the events were new primary cancers.

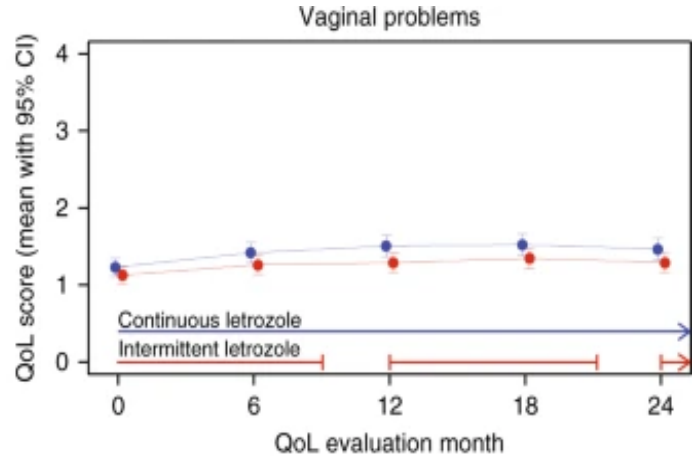


Optimal duration of extended endocrine therapy?

- SOLE Trial
  - Colleoni et al. Lancet Oncol. 2018;19(1):127.
- Additional five years of continuous letrozole versus an intermittent schedule in which the AI was given for nine months on followed by a three months off.
- There was no difference in DFS between the two schedules.
- Improved tolerance with the intermittent schedule.



Note: higher score indicates worse condition.



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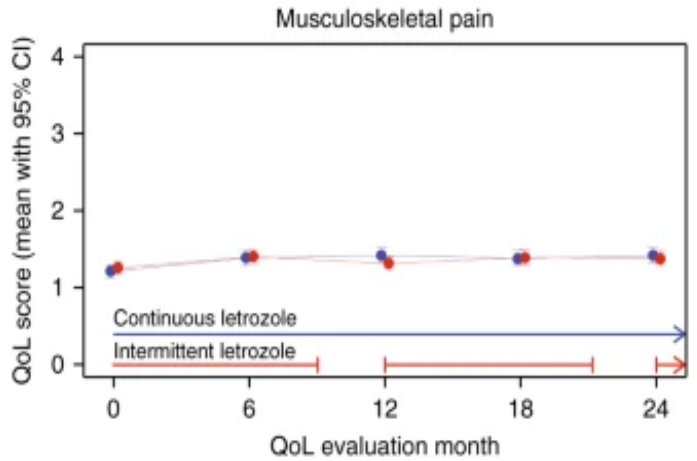

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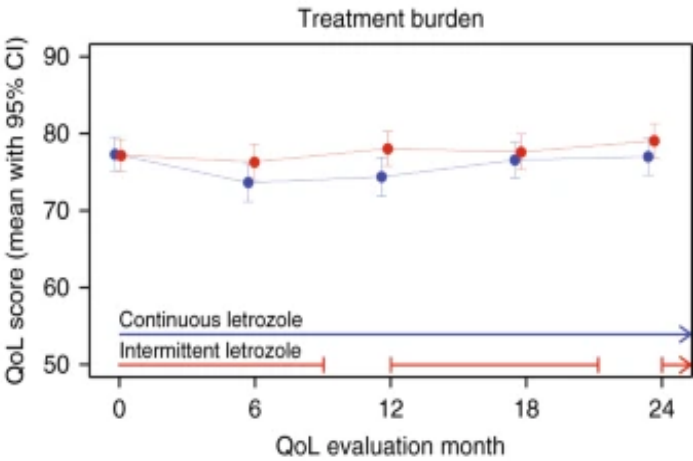
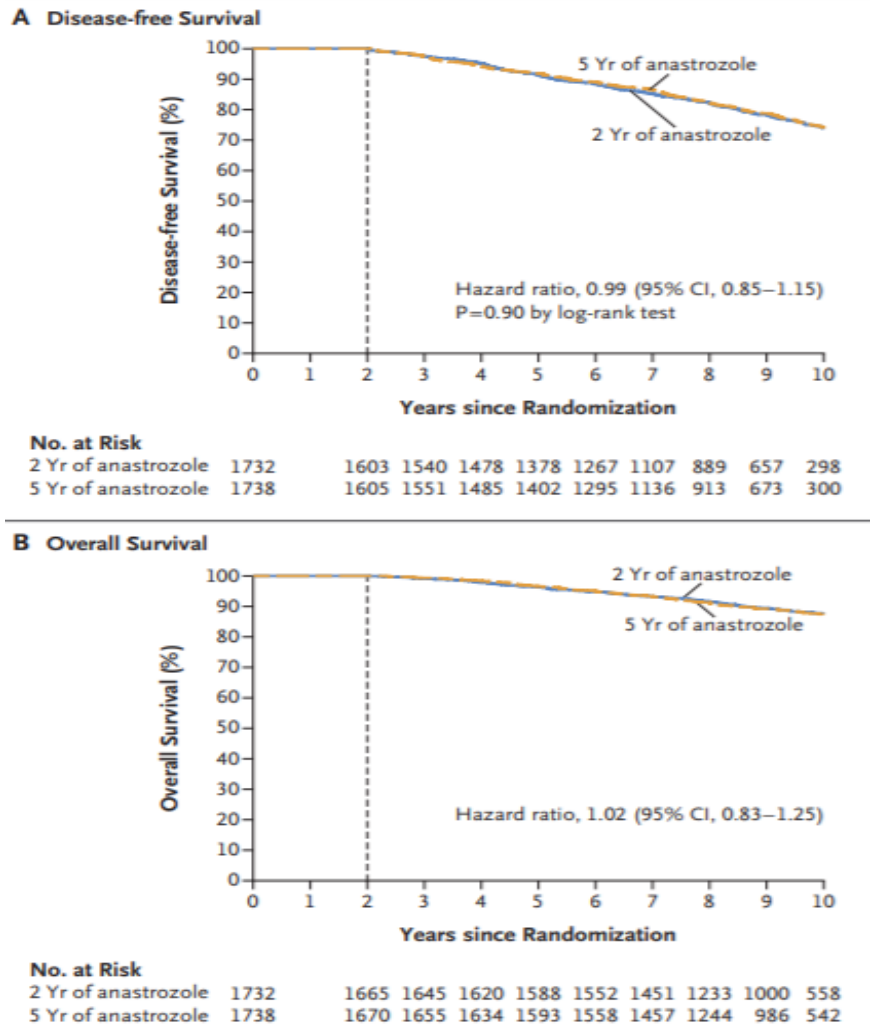


Note: higher score indicates worse condition.

Optimal duration of extended endocrine therapy?

- ABCSG-16
  - Gnant M et al. N Engl J Med. 2021
- After five years of adjuvant endocrine therapy , patients randomly assigned to two versus five years of anastrozole as extended adjuvant treatment.
- ~50% of the patients had already been on AI during the first five years of treatment
- Study cohort was very low risk (two-thirds with stage I disease)
- The two-year versus the five-year group experienced equivalent DFS.
- Distant recurrences occurred in ~ 5 percent in each group.
- Bone fractures occurred in 4.7 versus 6.3 percent, respectively (HR 1.35, 95% CI 1.00-1.84).



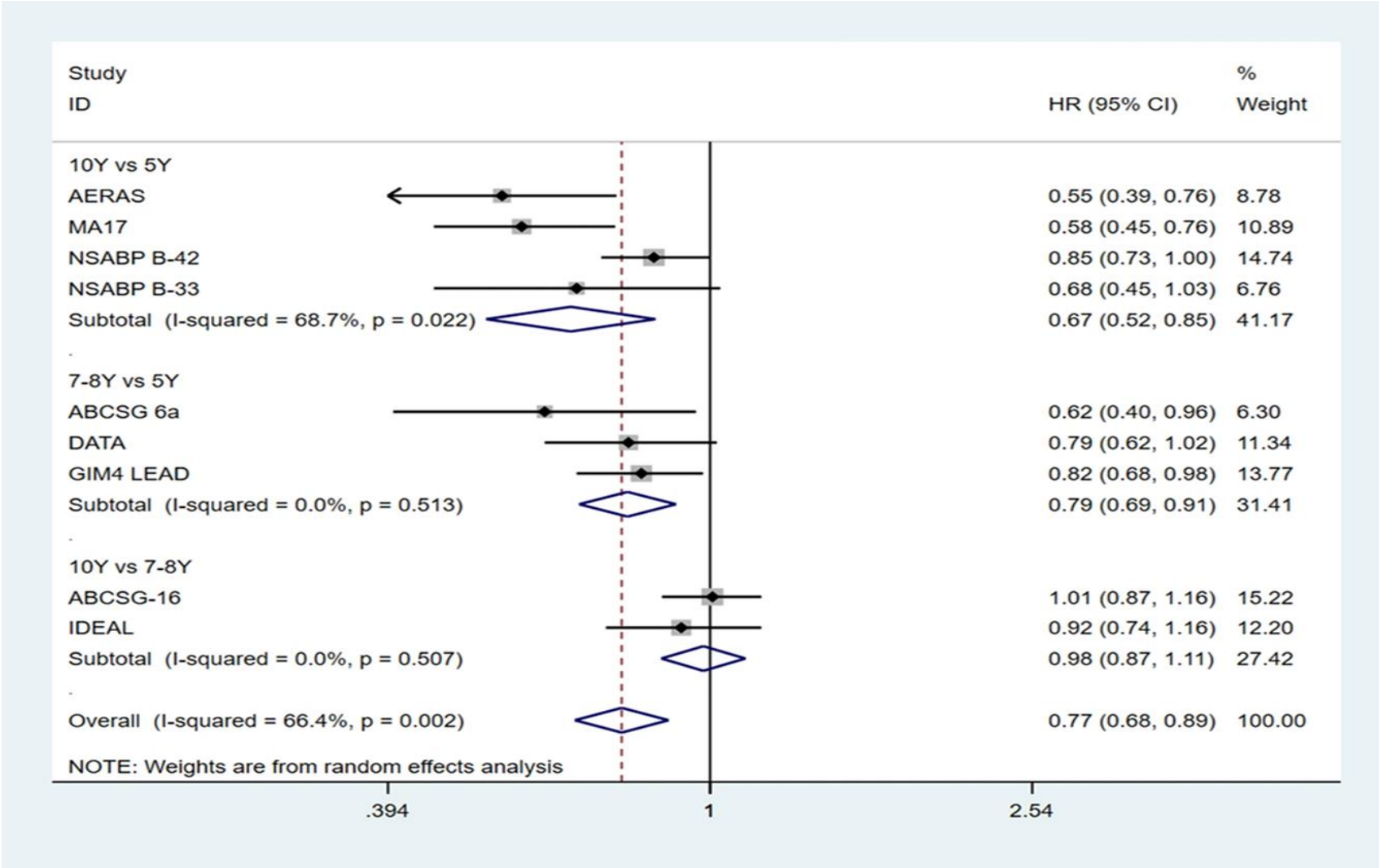
Optimal duration of endocrine therapy with extended aromatase inhibitors for postmenopausal patients with hormone receptor-positive breast cancer: a meta-analysis.

Chen et al. Breast Cancer. volume 28 (2021)

- 9 RCTs enrolling a total of 22,313 postmenopausal women with HR-positive breast cancer were included
  - Improvement in DFS when extending endocrine therapy from 5 to 7–8 years (HR = 0.79 [0.69, 0.91])
  - treated with only tamoxifen (HR = 0.40 [0.22, 0.73])
  - sequential tamoxifen followed by AI (HR = 0.82 [0.71, 0.95])
  - tumors that were node-positive (HR = 0.72 [0.56, 0.93])
  - estrogen receptor (ER) and progesterone receptor (PR) positive (HR = 0.61 [0.47, 0.78])
  - ≥ 2 cm in size (HR = 0.72 [0.51, 0.98])

Optimal duration of endocrine therapy with extended aromatase inhibitors for postmenopausal patients with hormone receptor-positive breast cancer: a meta-analysis.

Chen et al. Breast Cancer volume 28 (2021)

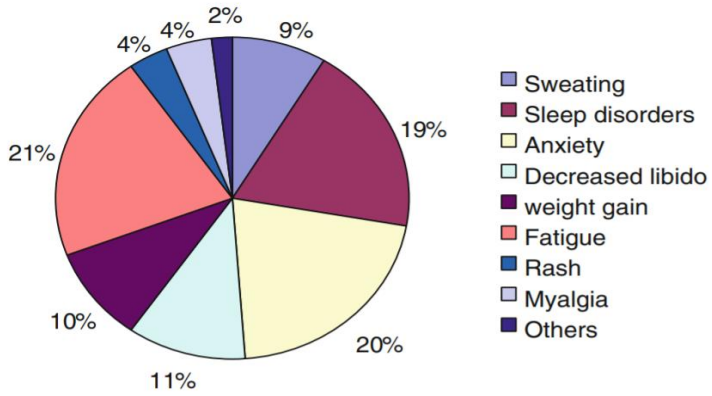


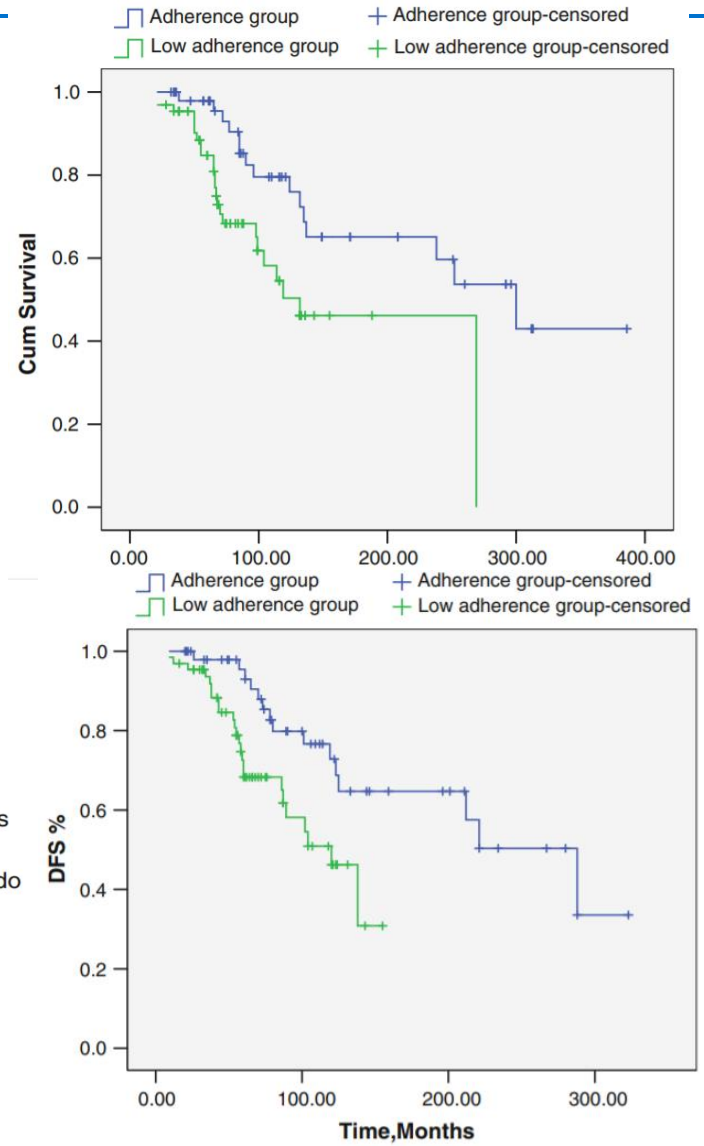
The role of genomic assays for selecting extended endocrine therapy

- Breast Cancer Index (BCI)
  - BCI (H/I) Low: For T1 and T2 HR pos, HER2 neg and pN0 tumors – the tumor is placed in the same prognostic category a T1a-T1b N0 M0 with no improvement in DFS or OS from extending endocrine therapy.
    - Noordhoek, et al. Clin Cancer Res 2021; 27:311-319
  - BCI (H/I) High: From secondary analyses of MA.17, Trans-aTTom, and IDEAL, patients with T1-3, pN0 or pN+ had significant improvements in DFS when adjuvant endocrine therapy was extended.

Male breast cancer: duration of endocrine therapy

- Based on data from the ATLAS trial – recommend 5 year minimum course of tamoxifen
- For higher risk disease – 7 vs 10 years of tamoxifen could be justified.
- Attrition high with adverse outcomes.
  - Xu S et al. Breast Cancer Res Treat. 2012 Nov;136(2):495-502.






City of Hope