HORMONAL THERAPY FOR BREAST CANCER PATIENTS

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Outline

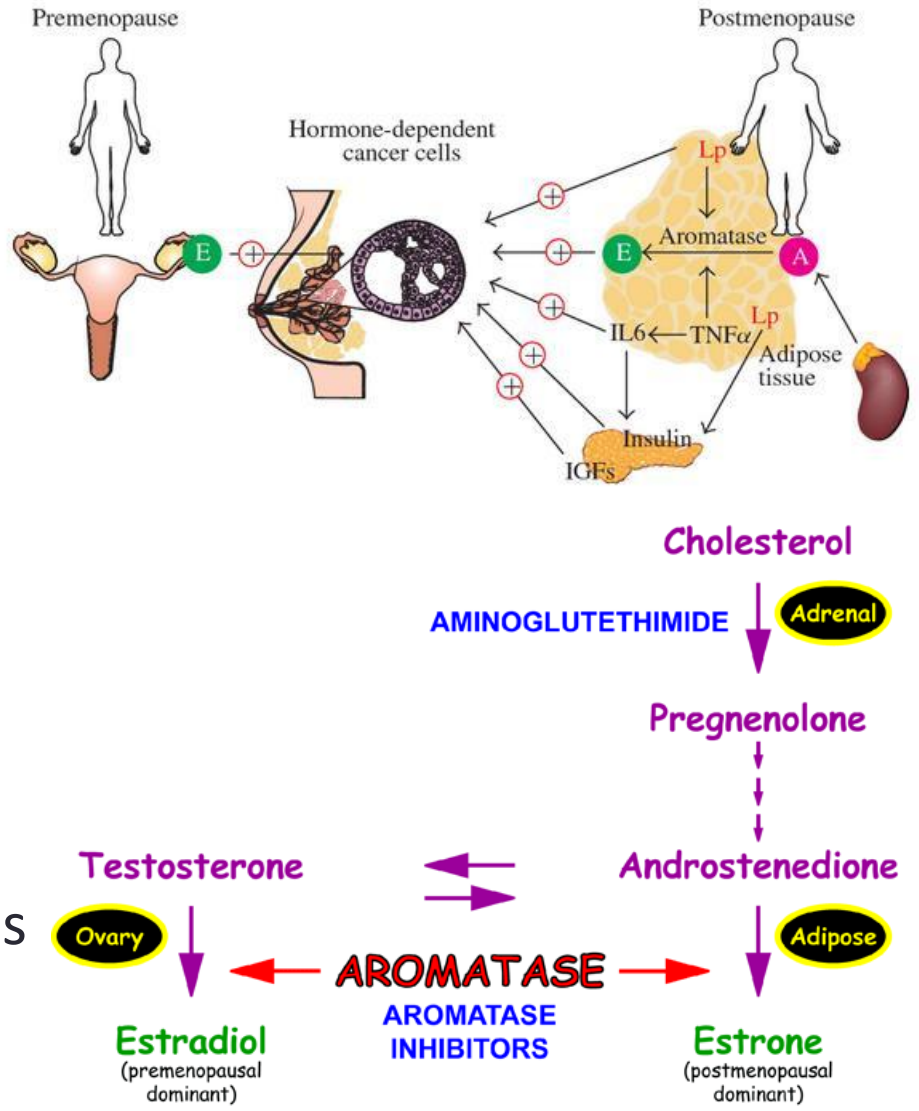
- Mechanism for hormonal therapy in breast cancer
- What are the hormonal therapies for breast cancer
- Tamoxifen
- Aromatase inhibitor (AI)
- Hormonal therapy for premenopausal women
- Hormonal therapy for postmenopausal women
- How to choose hormonal therapy
- Side effects of hormonal therapy
- Menopause
- Management of bone health after menopause

Sex hormones 性激素

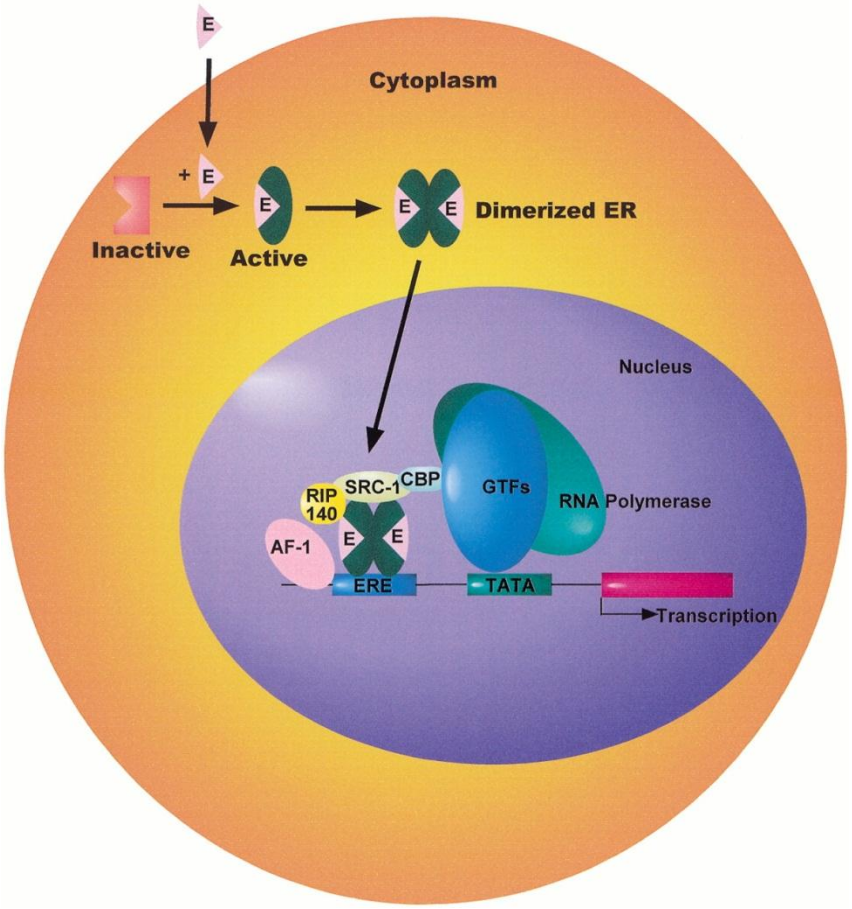
- 雌激素(Estrogen) and 孕激素(黄体酮 Progesterone)
- 雌激素的作用
  - Promotes the development and maintenance of female sex characteristics
  - Growth of long bones – stimulation of new bone formation, whereas it inhibits bone resorption
  - Cardioprotective effects – 'Female advantage'
  - Lipid metabolism - ↓ total cholesterol and LDL
- Progesterone plays a role in the menstrual cycle and pregnancy

Production of estrogen

- In premenopausal women, the ovaries are the predominant source of estrogen, only small proportion comes from peripheral organs
- In contrast, the little estrogen produced in postmenopausal women comes predominantly from aromatization of adrenal and ovarian androgens in extragonadal tissues such as liver, muscle and fat tissues

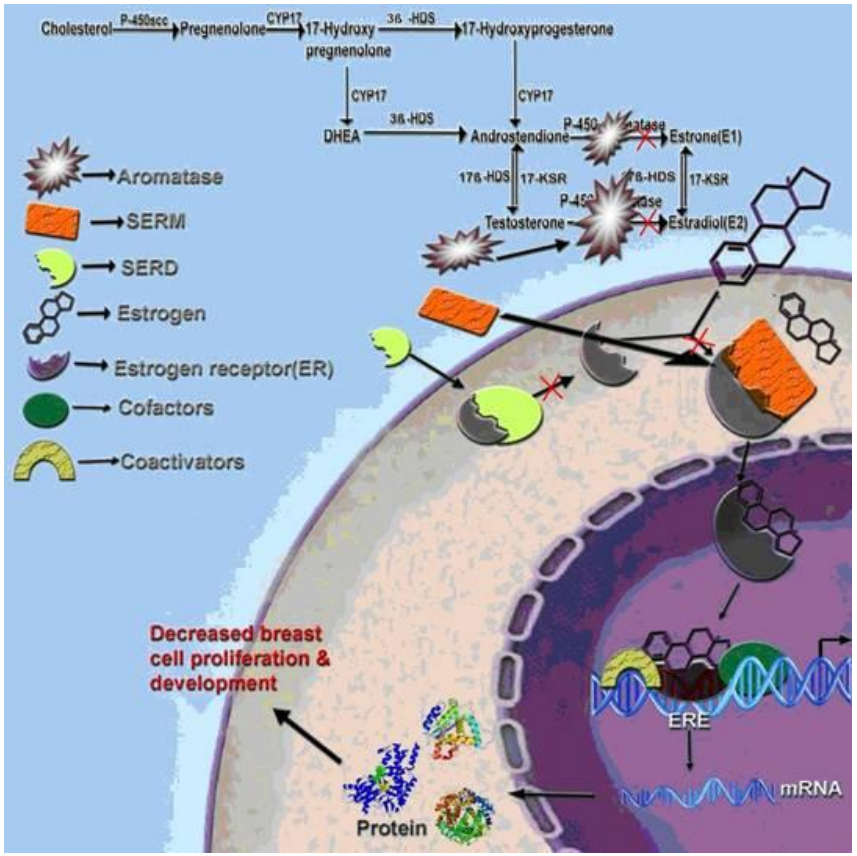


Role of estrogen and estrogen receptor in breast cancer



- Estrogen and progesterone can also promote the growth of some BC, which are called hormone-sensitive (or hormone-dependent) BC
- Hormone-sensitive BC cells contain proteins known as hormone receptors that become activated when hormones bind to them
- The activated receptors cause changes in the expression of specific genes, which can lead to the stimulation of cell growth
- Tumours that are hormone-insensitive do not respond to hormone therapy
- Approximately 70 percent of breast cancers are ER-positive

Types of hormonal therapy



- Blocking ovarian function – LHRHa
- Blocking estrogen production – AIs
- Blocking estrogen's effects
  - Selective estrogen receptor modulators (SERMs)
    - Tamoxifen
    - Raloxifen
  - Other antiestrogen drugs
    - Fulvestrant (SERD)

Hormone therapy for breast cancer is not the same as female hormone replacement therapy (HRT), in which hormones are given to reduce the symptoms of menopause

FDA approved indication of hormonal therapy in BC

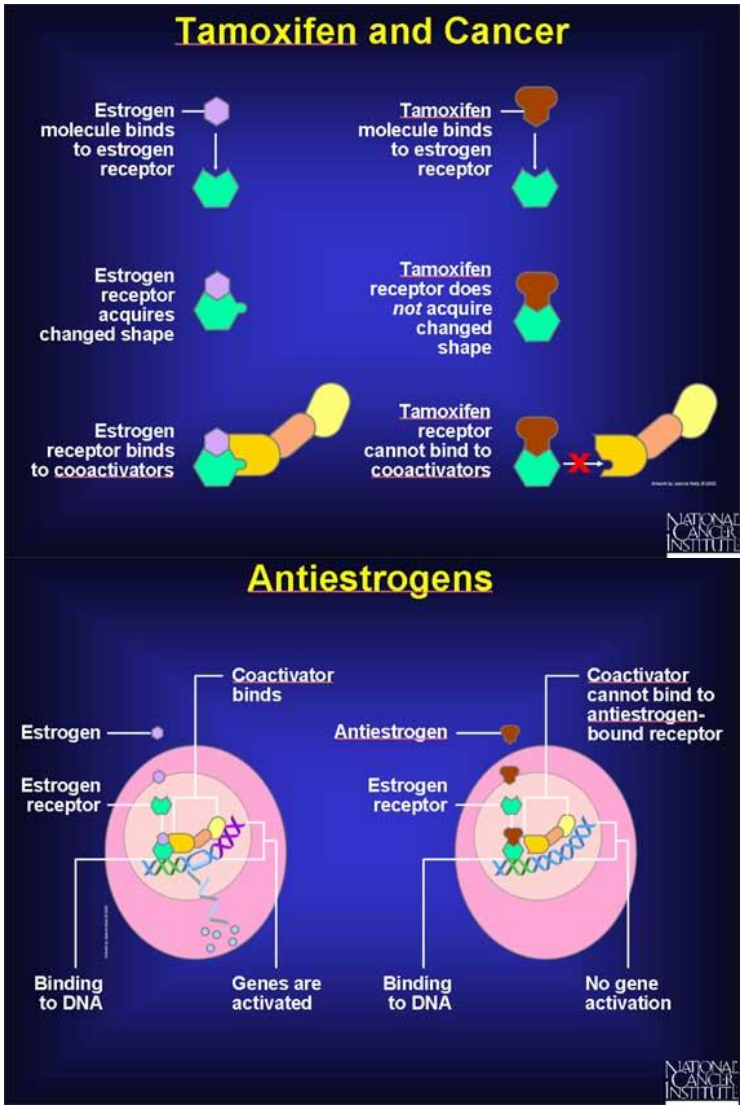
	Prevention	Adjuvant for early BC	Metastatic	Neoadjuvant
Tamoxifen	Yes[1]	Yes[2]	Yes	No
AIs		Yes[3]	Yes	No
Fulvestrant			Yes[4]	No
Raloxifen	Yes[1]			No
Toremifene			Yes	No

1. Tamoxifen is approved for use regardless of menopausal status. Raloxifene is approved for use only in postmenopausal women
2. Premenopausal and postmenopausal women (and men)
3. Postmenopausal women
4. Postmenopausal women with metastatic ER-positive BC after treatment with other antiestrogens

Ovarian ablation or ovarian function suppression

- Ovarian ablation –
  - Surgical oophorectomy
  - Radiation
    - may be incomplete and delayed, biochemical verification is required
- Ovarian function suppression
  - Gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LHRH) agonists
  - Interfere signals from pituitary gland that stimulate the ovaries to produce estrogen
  - Time-limited, reversible
  - Goserelin (Zoladex®) and leuprolide (Lupron®)

Tamoxifen – 三苯氧胺 (他莫昔芬)



- Acting as anti-estrogen by inhibiting the binding of estrogen to estrogen receptor (ER)
- More properly referred to as selective estrogen-receptor modulators (SERM)
- Because SERMs bind to estrogen receptors, they can potentially also mimic estrogen effects (i.e., serve as estrogen agonists)

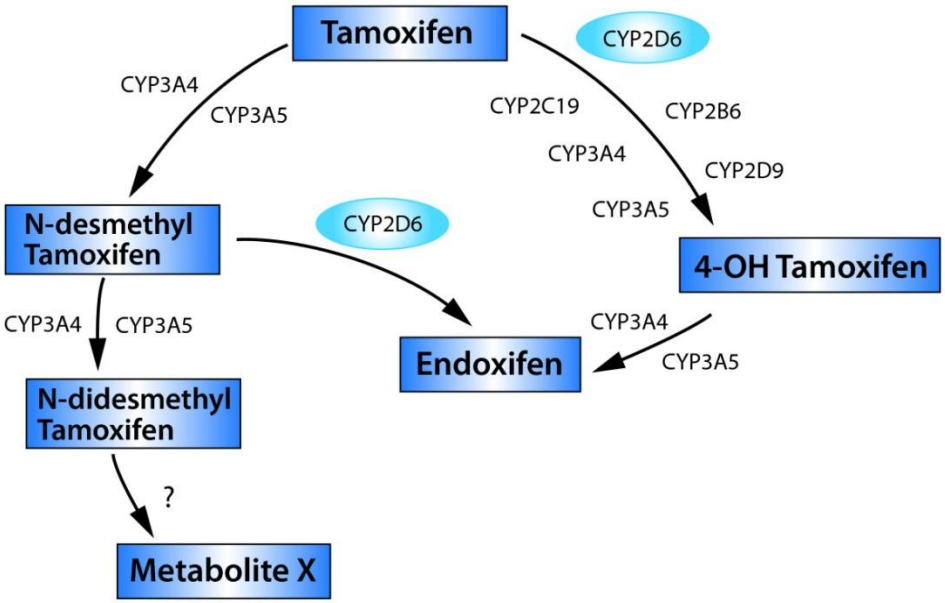
SERM (選擇性雌激素受體調節劑)

- A drug that acts like estrogen on some tissues but blocks the effect of estrogen on other tissues
- Examples of SERMS approved by the FDA are tamoxifen (Nolvadex®), raloxifene (Evista®), and toremifene (Fareston®)
- Most SERMs behave as estrogen antagonists in some tissues and as estrogen agonists in other tissues. For example, tamoxifen blocks the effects of estrogen in breast tissue but acts like estrogen in the uterus and bone

Tamoxifen

- Tamoxifen has been used for more than 30 years to treat hormone receptor-positive BC
- In adjuvant setting, tamoxifen decrease disease recurrence and mortality rates by as much as 50% and 30% respectively
- 7-10% of women with BC may not receive the full medical benefit from taking tamoxifen due to their unique genetic make-up
- At this time, based on current data, NCCN does not endorse routine CYP2D6 testing for women being considered for tamoxifen therapy

Metabolism of tamoxifen



- Tamoxifen itself is a prodrug, having relatively little affinity for its target protein, the estrogen receptor
- It is metabolized in the liver by the cytochrome P450 isoform CYP2D6 and CYP3A4 into active metabolites such as 4-hydroxytamoxifen (afimoxifen) and N-desmethyl-4-hydroxytamoxifen (endoxifen) which have 30-100 times more affinity with the estrogen receptor than tamoxifen itself
- Endoxifen is considered the most important metabolite because its plasma concentrations are several times higher than those of 4-hydroxytamoxifen

Major drug classes with known CYP2D6 inhibitory activity

Table 3. Major Drug Classes Divided by Known CYP2D6 Inhibitory Activity

Class	Moderate-to-Potent Inhibitors With Clearly Demonstrated or Expected In Vivo Inhibition†	Weak-to-Moderate Inhibitors That Have Demonstrated or Could Potentially Have Some In Vivo Effect‡	Alternative Drugs Expected to Have Little In Vivo Inhibition§
SSRI/SNRIs	Paroxetine* Fluoxetine* Bupropion Duloxetine	Sertraline* Citalopram* Fluvoxamine	Venlafaxine* Desvenlafaxine Reboxetine Escitalopram Mirtazapine
Tricyclic antidepressants		Clomipramine Doxepin Desipramine Imipramine Amitriptyline Nortriptyline	
Antipsychotics	Thioridazine Perphenazine Pimozide	Chlorpromazine Fluphenazine Haloperidol	Thiothixene Clozapine Risperidone Clozapine Olanzapine Ziprasidone Quetiapine
Cardiac medications	Quinidine Ticlopidine	Amiodarone Nicardipine Verapamil Amlodipine Felodipine Nifedipine	Diltiazem
Medications for infectious diseases	Terfenadine Quinidine‖	Ritonavir Halofantrine Chloroquine	Indinavir Saquinavir Nelfinavir Delavirdine Nevirapine Efavirenz
H2 blockers		Cimetidine	Ranitidine
H1 blockers¶		Clemastine Tripelennamine Promethazine Hydroxyzine Diphenylpyraline	Chlorpheniramine Cetirizine Loratadine
Miscellaneous medications	Cinacalcet	Celecoxib	Gabapentin

Abbreviations: CYP2D6, cytochrome P450 2D6; SSRI, selective serotonin reuptake inhibitor; SNRI, selective noradrenergic reuptake inhibitor; AUC, area under the concentration-time curve.

*Medications with in vivo data that demonstrate an effect on endoxifen concentrations when coprescribed with tamoxifen.

†Medications classified as moderate-to-potent inhibitors have demonstrated in vivo inhibition of CYP2D6 substrates with an increase in the plasma AUC of the substrate by at least two-fold or higher and/or in vitro inhibition using human liver microsome systems with in vitro inhibition constant (Ki) values ≤ 1 μmol/L. These medications are expected to have or have demonstrated phenotypic conversion of extensive metabolizers to poor metabolizers and significant reduction in endoxifen levels. They should not be administered to women receiving tamoxifen for prolonged periods of time.

‡Medications classified as weak-to-moderate inhibitors have demonstrated in vivo inhibition of CYP2D6 substrates with an increase in the plasma AUC of the substrate by less than two-fold and/or in vitro inhibition using human liver microsome systems with Ki values in the range of 2 to 10 μmol/L. Although these medications have either demonstrated lesser reductions in endoxifen levels, or could potentially result in reduction of endoxifen levels, it is unclear what the clinical importance of such reductions may be.

§Medications classified as "alternative drugs, expected to have little in vivo inhibition" are not expected to have any effect on endoxifen levels.

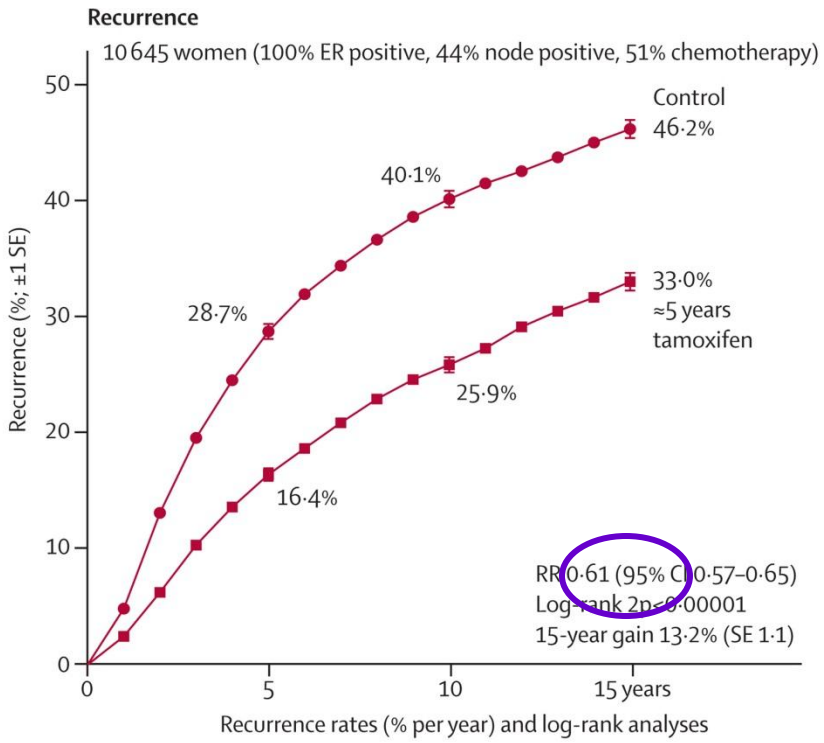
SSRI / SNRI

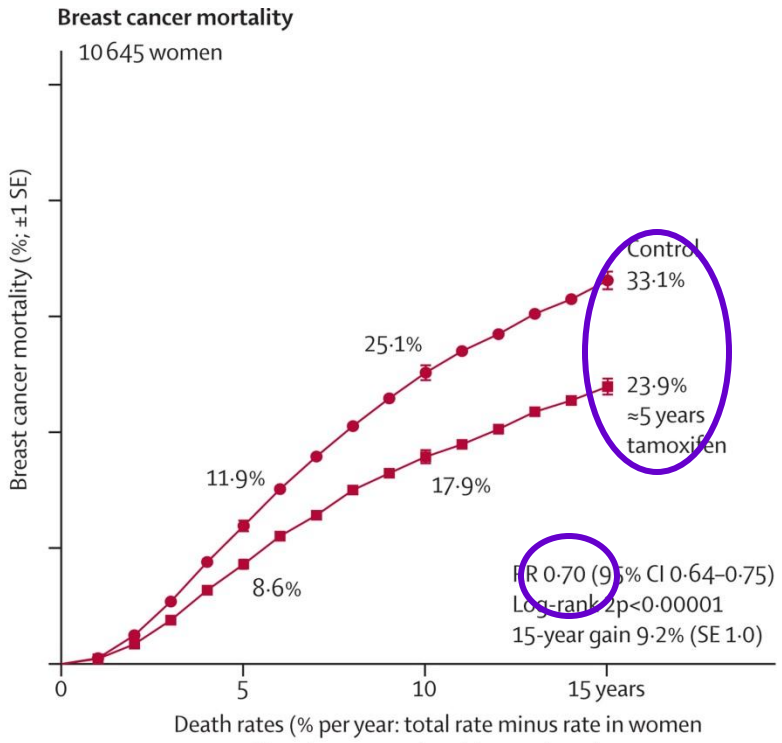
- SSRI: Selective serotonin reuptake inhibitor
  - SSRIs are widely used in the treatment of depression, anxiety disorders and some personality disorders. They act by inhibiting the reuptake of serotonin into the presynaptic cell, increasing the levels of serotonin available for binding to postsynaptic receptors and/or prolonging the effects of serotonin
  - The SSRIs are
    - Fluoxetine (brand names Prozac; Oxactin)
    - Paroxetine (Seroxat)
    - Citalopram (Cipramil)
    - Sertraline (Lustral)
- SNRI: Selective serotonin and noradrenaline reuptake inhibitor
  - Dual action serotonin and noradrenaline reuptake inhibitors are a class of antidepressant drug used to treat major depression and other disorders
  - They are a newer class of drug than SSRIs, but act in a similar way, altering neurotransmitter levels in the brain, or prolonging their effects
  - SNRIs act particularly on serotonin and noradrenaline
- SSRIs and SNRIs effectively decrease vasomotor symptoms in healthy menopausal women and women with breast cancer, on or off endocrine therapy

Adjuvant hormone – ET

- ET for premenopausal women
  - Tamoxifen
  - Ovarian Function Suppression (OFS)
  - (Tam + OFS)
  - (OFS + AI)
- ET for postmenopausal women
  - Tamoxifen
  - AI
    - Upfront
    - Switching
    - Extended

Effects of ~ 5 yr Tam on 15-yr probabilities of recurrence and of BC mortality, ER+ disease





	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

Yearly rate of BC mortality reduced by about 1/3 (RR 0.7, [0·05], p<0·00001) throughout first 15 yrs with highly significant benefit during each of years 0-4, 5-9 and 10-14. Absolute mortality difference only 3% at yr 5, but three times as great 24% vs. 33% by yr 15

EBCTCG. Lancet 2011; 378: 771–84

Benefit of 5 yr adjuvant Tam

- In ER+ disease, 5 yr Tam substantially reduced **recurrence rates** throughout the first 10 years
  - RR 0.53 [SE 0.03] during years 0-4
  - RR 0.68 [0.06] during years 5-9 [both 2p<0.00001)
  - But RR 0.97 [0.10] during years 10-14, suggesting no further gain or loss after year 10
- Even in marginally ER+ disease, the recurrence reduction was substantial (RR 0.67 [0.08])
- In ER+ disease, the RR was approximately independent of PR status (or level), age, nodal status, or use of chemo

Tamoxifen – Protection on contralateral breast

- Tam reduced contralateral BC incidence
- The absolute (and proportional) decrease was independent of age, with 15 yr incidence on 6.5% (tamoxifen) vs. 9.8% (control) in ER+ disease, absolute reduction 3.2%
- In ER-poor disease, the 15 yr incidence was 7.1% in both treatment groups, absolute reduction 0.1% [1.1]

AIs – Aromatase inhibitors (芳香化酶抑制劑)

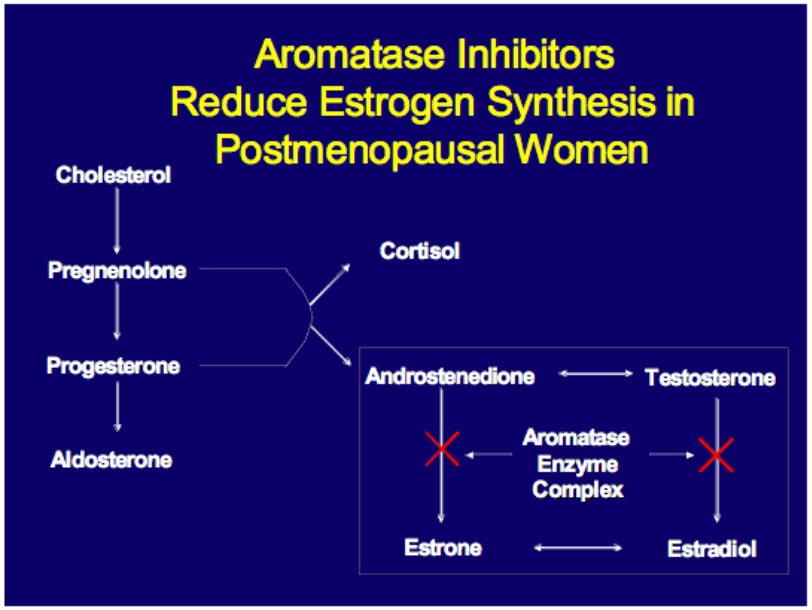
- Aromatase is an enzyme of cytochrome P-450, which the body uses to make estrogen in the ovaries and in other tissues. It is present at lower levels in several non glandular tissues including subcutaneous fat, liver, muscle, brain, normal breast, and breast-cancer tissue
- AI markedly suppresses the plasma estrogen levels in postmenopausal women by inhibiting or inactivating aromatase
- Indicated for post-menopausal women hormone receptor positive BC
- Not appropriate in pre-menopausal – presence of ovarian derived estrogens because the ovaries in premenopausal women produce too much aromatase for the inhibitors to block effectively

Aromatase inhibitors - AIs

AIs → Inhibits → **Aromatase**

Androgens → Biosynthesis → **Estradiol**

Figure 1. Mechanism of Action of Aromatase Inhibitors.



Growth stimulation

Estrogen dependent breast cancer

Indication of AIs

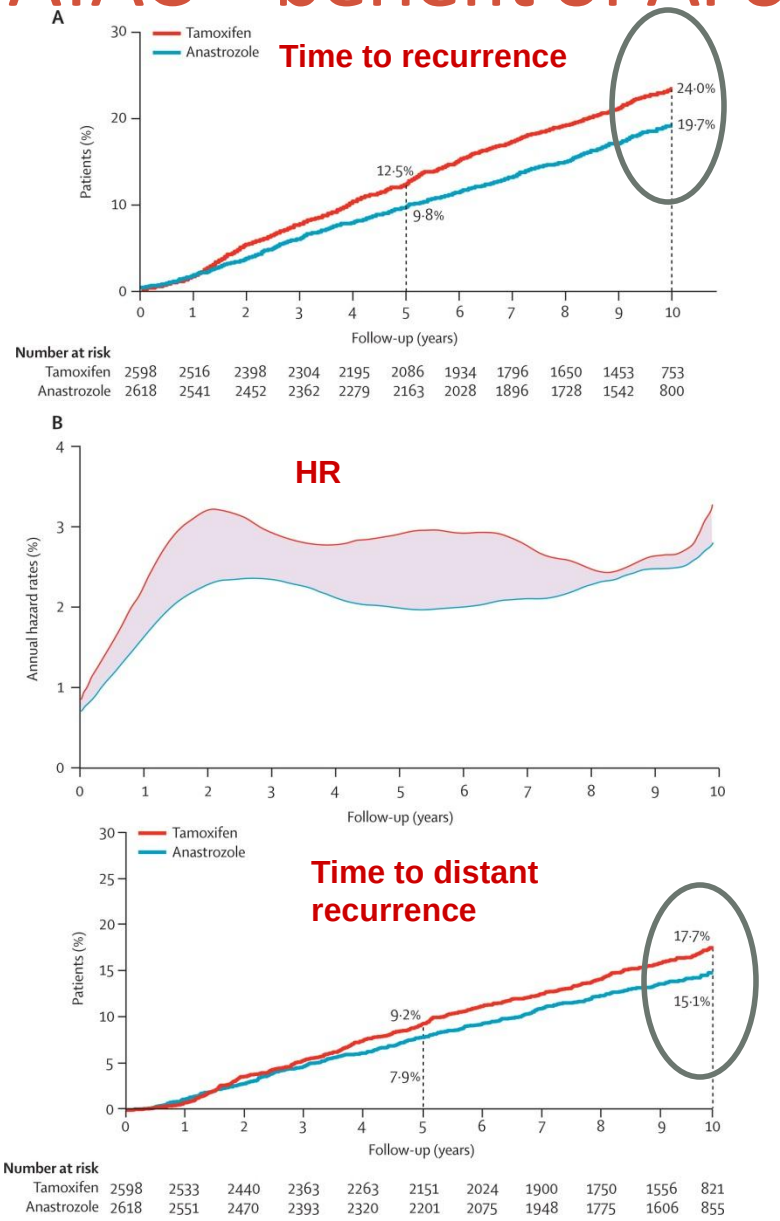
- For ER+ (雌激素受體呈陽性) postmenopausal patients
  - Primary or upfront treatment instead of tamoxifen
  - Sequential therapy after 2-3 yr of tamoxifen
  - Extended therapy after 5 yr of tamoxifen

10-year analysis of the ATAC trial

	Full study population A=3125 T= 3116			Hormone receptor +ve pts A=2618, T=2598		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
DFS	**0.91**	**0.83-0.99**	**0.04**	**0.86**	**0.78-0.95**	**0.003**
Time to recurrence	**0.84**	**0.75-0.93**	**0.001**	**0.79**	**0.70-0.89**	**0.0002**
Time to distant recurrence	**0.87**	**0.77-0.99**	**0.03**	**0.85**	**0.73-0.98**	**0.02**

Lancet Oncol. 2010 Dec;11(12):1135-41

ATAC – benefit of AI over tamoxifen



- In HR+ patients, those receive anastrozole had a 4.3% lower absolute rate of BC recurrence after 10 yrs, and a 2.6% lower absolute rate of distant metastasis
- Absolute differences increased over time (2·7% at 5 years and 4·3% at 10 years), although the carryover effect – in which benefits extend beyond the treatment period – began to wane after about 8 years

Lancet Oncol. 2010 Dec;11(12):1135-41

ATAC – Deaths in the full study population

	Anastrozole n=3,125 (%)	Tamoxifen n=3,116 (%)
Total deaths	734 (23.5)	747 (24)
Deaths after recurrence	395 (12.6)	441 (14.2)
Deaths without recurrence	339 (10.8)	306 (9.8)
Cardiovascular	91 (2.9)	95 (3)
Cerebrovascular	33 (1.1)	36 (1.2)
Other cancer	108 (3.5)	82 (2.6)
Other	107 (3.4)	93 (3)

The number of patient deaths, with or without breast cancer recurrence, was similar in the two groups after 10 years of follow-up. Thus, treatment with anastrozole did not improve overall survival compared with tamoxifen

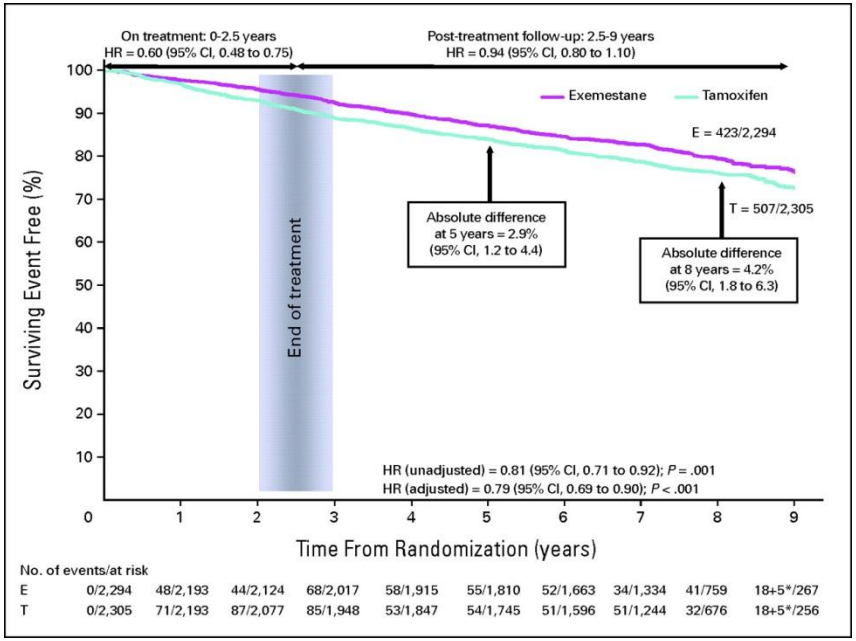
Lancet Oncol. 2010 Dec;11(12):1135-41

Comment on results of ATAC

- Limited magnitude of the average benefit reported in the 10-year analysis of ATAC strongly suggests that only a few patients derive actual benefit from anastrozole – the majority might not
- Evidence base for individualized treatment decisions remains unclear
  - ?Limited benefit of AI for PR+ tumour, pts with very low risk of recurrence
  - ?For pts with HER2+ or enzymatic variations in CYP2D6 metabolism, tamoxifen might not be the optimum treatment

10 years of ATAC: one question answered, many others unresolved: Gnant M. Lancet Oncol. 2010 Dec;11(12):1109-10

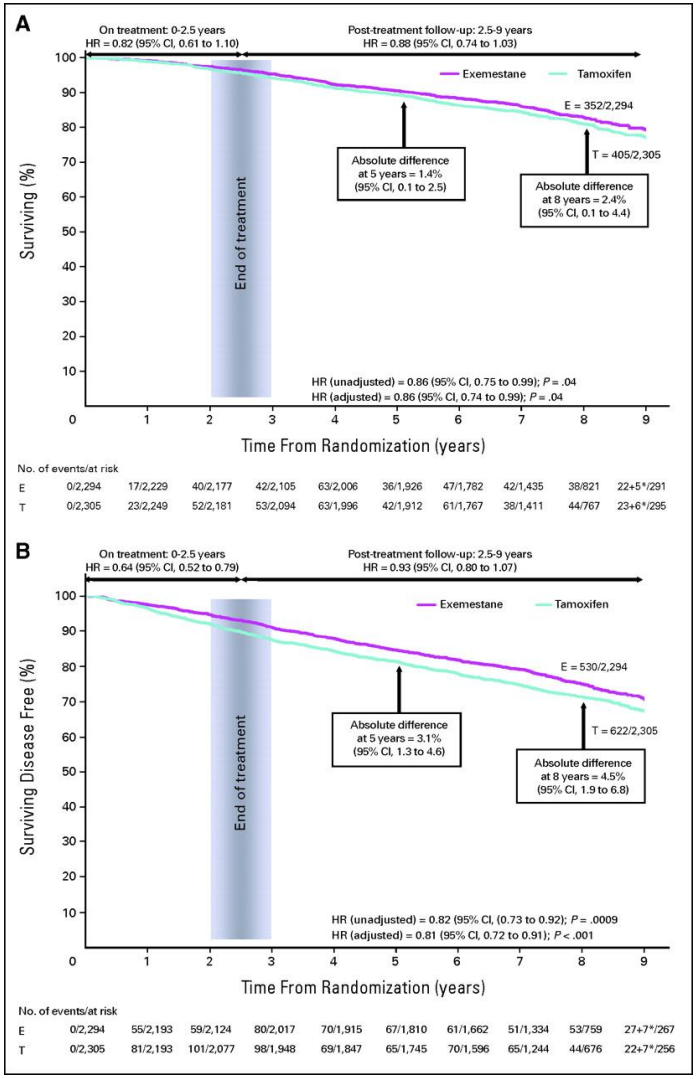
IES – results of 91 month median follow up



- Breast cancer free survival in ER+/unknown population, HR 0.6
- On-treatment benefit was not lost post-treatment, but there was no additional gain once treatment had ceased (HR 0.94, p=0.6)

JM Bliss, et al. J Clin Oncol 2011;30:709-717

IES – OS and DFS



- Patient who switched to exemestane had
  - An absolute difference in survival outcome at 8 yrs of 2.4%, 14% reduction in risk of death (HR 0.86)
  - Absolute difference in DFS of 4.5% (HR 0.81)

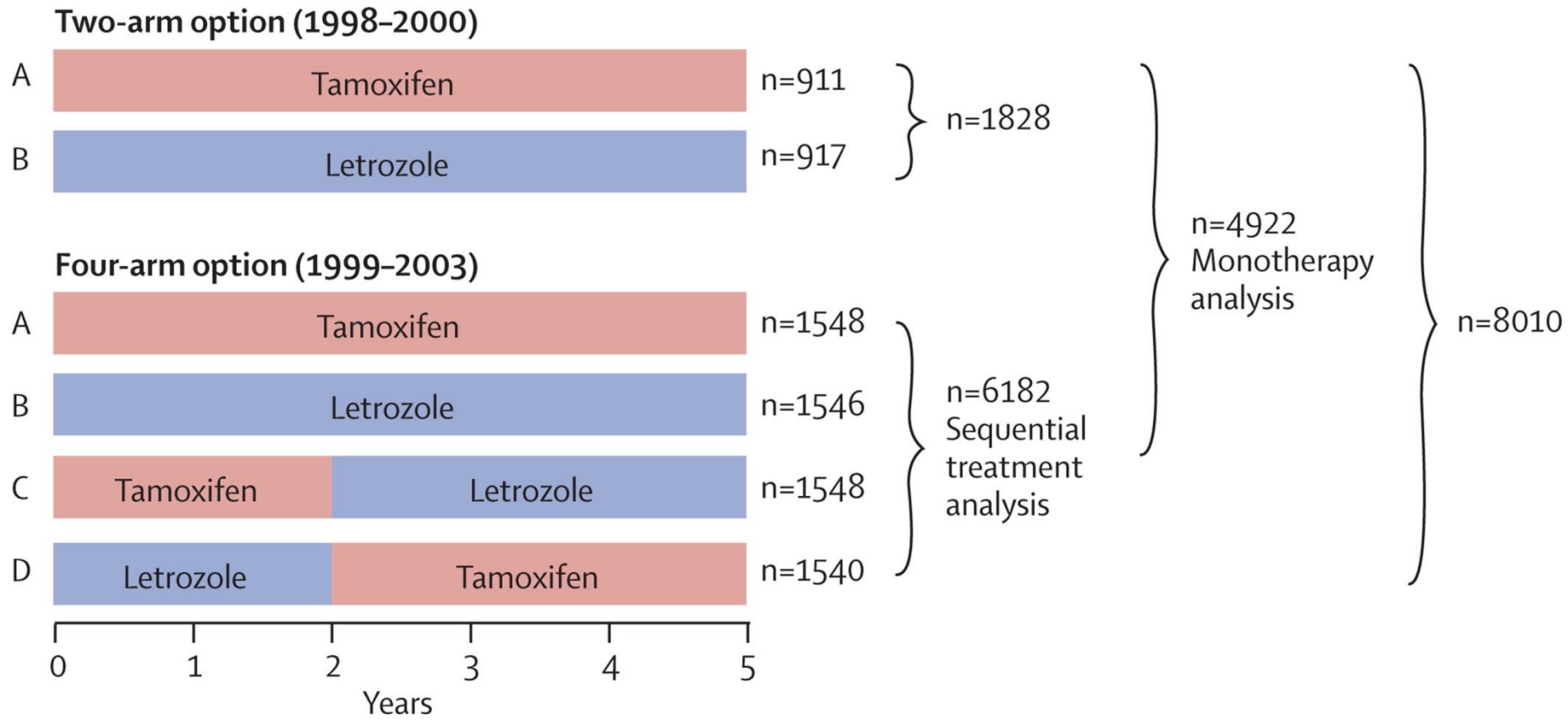
JM Bliss, et al. J Clin Oncol 2011;30:709-717

Update results of IES

- Protective effect of switching to exemestane compared with continuing on tamoxifen on risk of relapse or death was maintained for at least 5 years post-treatment and was associated with a continuing beneficial impact on overall survival

JM Bliss, et al. J Clin Oncol 2011;30:709-717

BIG 1-98 8.1 yr median follow up



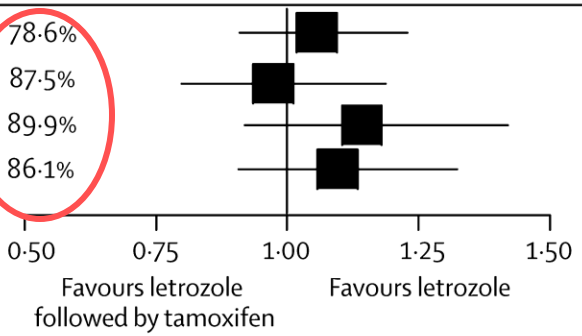
Two analytic populations: the monotherapy population (pts randomly assigned in the two-arm or four-arm option to receive either Tam (n=911+1548=2459) or letrozole (n=917+1546=2463) for 5 yrs) and the sequential treatment population (pts randomized in the four-arm option

Meredith MR et al. Lancet Oncol 2011;12:1101-08

Sequential treatment analysis

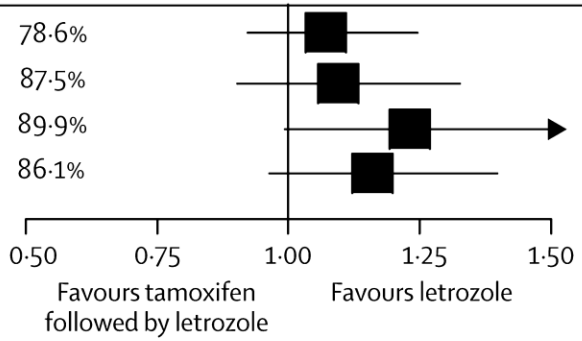
A

	Letrozole followed by tamoxifen (n=1540)			Letrozole (n=1546)			HR (95% CI)	p value
	Events	5-year percentage	8-year percentage	Events	5-year percentage	8-year percentage		
DFS	348	87·4%	77·8%	329	87·6%	78·6%	1·06 (0·91–1·23)	0·48
OS	194	93·6%	87·7%	197	93·3%	87·5%	0·97 (0·80–1·19)	0·79
DRFI	173	93·4%	88·7%	151	94·1%	89·9%	1·14 (0·92–1·42)	0·24
BCFI	226	92·4%	85·3%	206	92·5%	86·1%	1·10 (0·91–1·32)	0·34



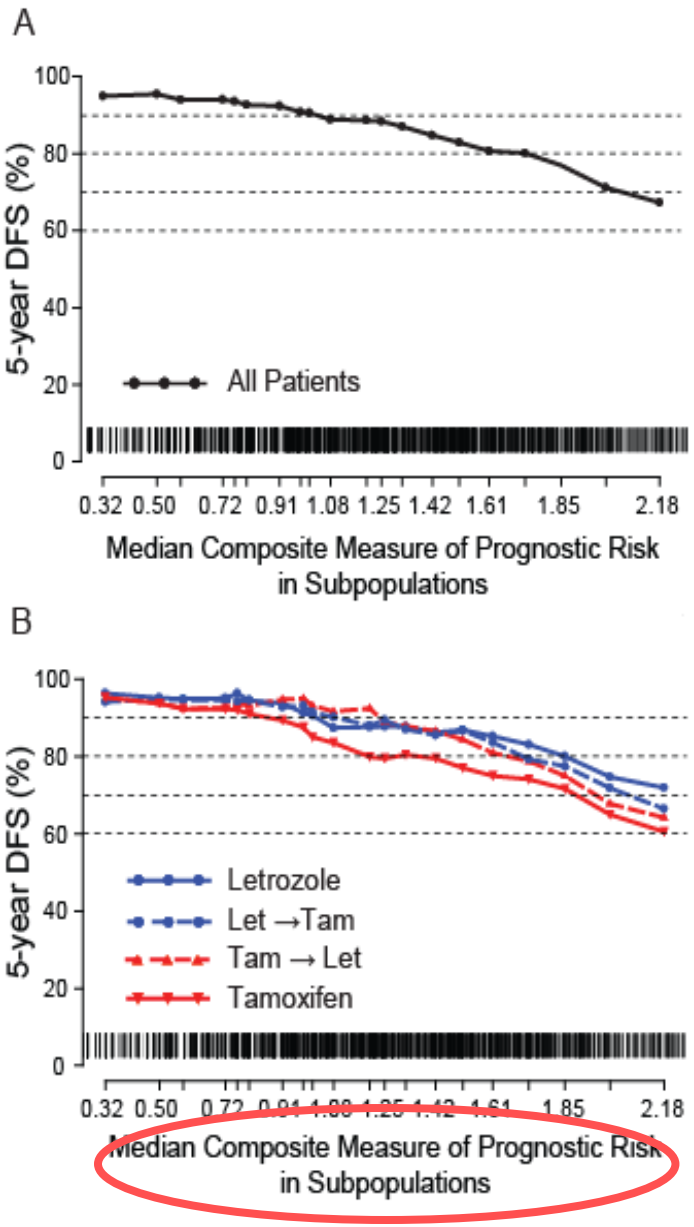
B

	Tamoxifen followed by letrozole (n=1548)			Letrozole (n=1546)			HR (95% CI)	p value
	Events	5-year percentage	8-year percentage	Events	5-year percentage	8-year percentage		
DFS	353	86·2%	77·3%	329	87·6%	78·6%	1·07 (0·92–1·25)	0·36
OS	217	92·5%	85·9%	197	93·3%	87·5%	1·10 (0·90–1·33)	0·36
DRFI	186	92·3%	88·1%	151	94·1%	89·9%	1·23 (0·99–1·53)	0·06
BCFI	239	90·4%	84·3%	206	92·5%	86·1%	1·16 (0·96–1·40)	0·12



At a median fu of 8 yr for the comparison of the sequential groups with letrozole monotherapy, there were no statistically significant differences in any of the four endpoints for either sequence

Which patients benefit most from AI



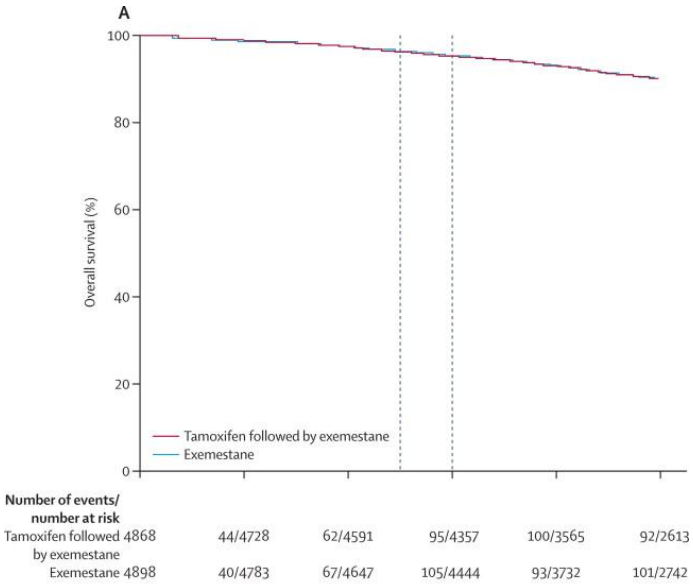
- Non-parametric Subpopulation Treatment Effect Pattern Plot (STEPP)
- All 4 treatments has similar 5 yr DFS for pt at lowest risk (left end of x-axis), the 3 letrozole-containing treatments had similar 5 yr DFS for intermediate risk (middle), where pts given letrozole for 5 yr had better outcome for those at highest risk
- Upfront letrozole might be reasonable for pts at high risk for early relapse, but sequential…useful for others considering tolerability

BIG 1-98 8.1 yr median follow up

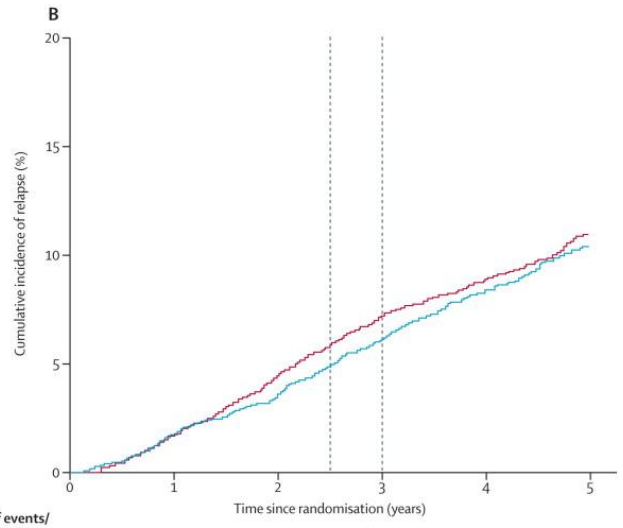
- For postmenopausal women with endocrine-responsive early breast cancer, a reduction in breast cancer recurrence and mortality is obtained by letrozole monotherapy when compared with Tam mono
- Sequential treatments involving Tam and Letrozole do not improve outcome c/w letrozole mono, but might be useful strategies when considering an individual patient's risk of recurrence and treatment tolerability

Meredith MR et al. Lancet Oncol 2011;12:1101-08

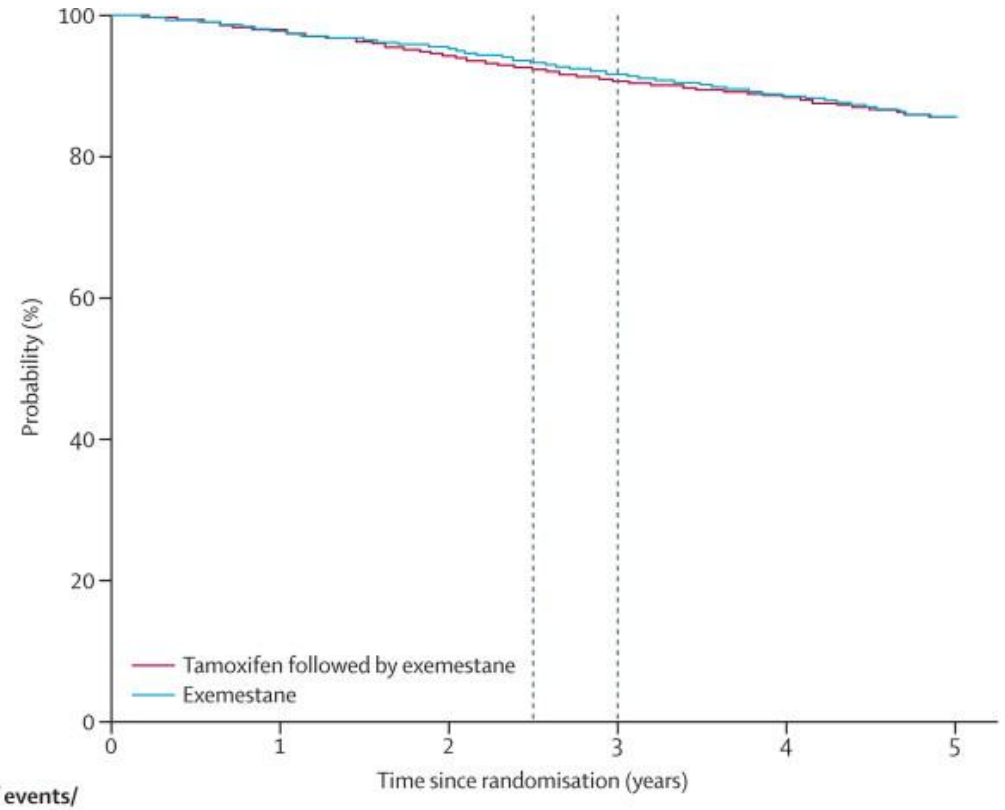
TEAM: Tam followed by exemestane vs. exemestane



Number of events/ number at risk						
Tamoxifen followed by exemestane	4868	44/4728	62/4591	95/4357	100/3565	92/2613
Exemestane	4898	40/4783	67/4647	105/4444	93/3732	101/2742



Number of events/ number at risk						
Tamoxifen followed by exemestane	4868	82/4660	131/4436	124/4140	73/3377	66/2529
Exemestane	4898	85/4716	87/4533	117/4272	100/3575	67/2564



Number of events/ number at risk						
Tamoxifen followed by exemestane	4868	111/4660	160/4436	155/4140	108/3377	100/2529
Exemestane	4898	109/4716	117/4533	166/4272	133/3575	107/2564

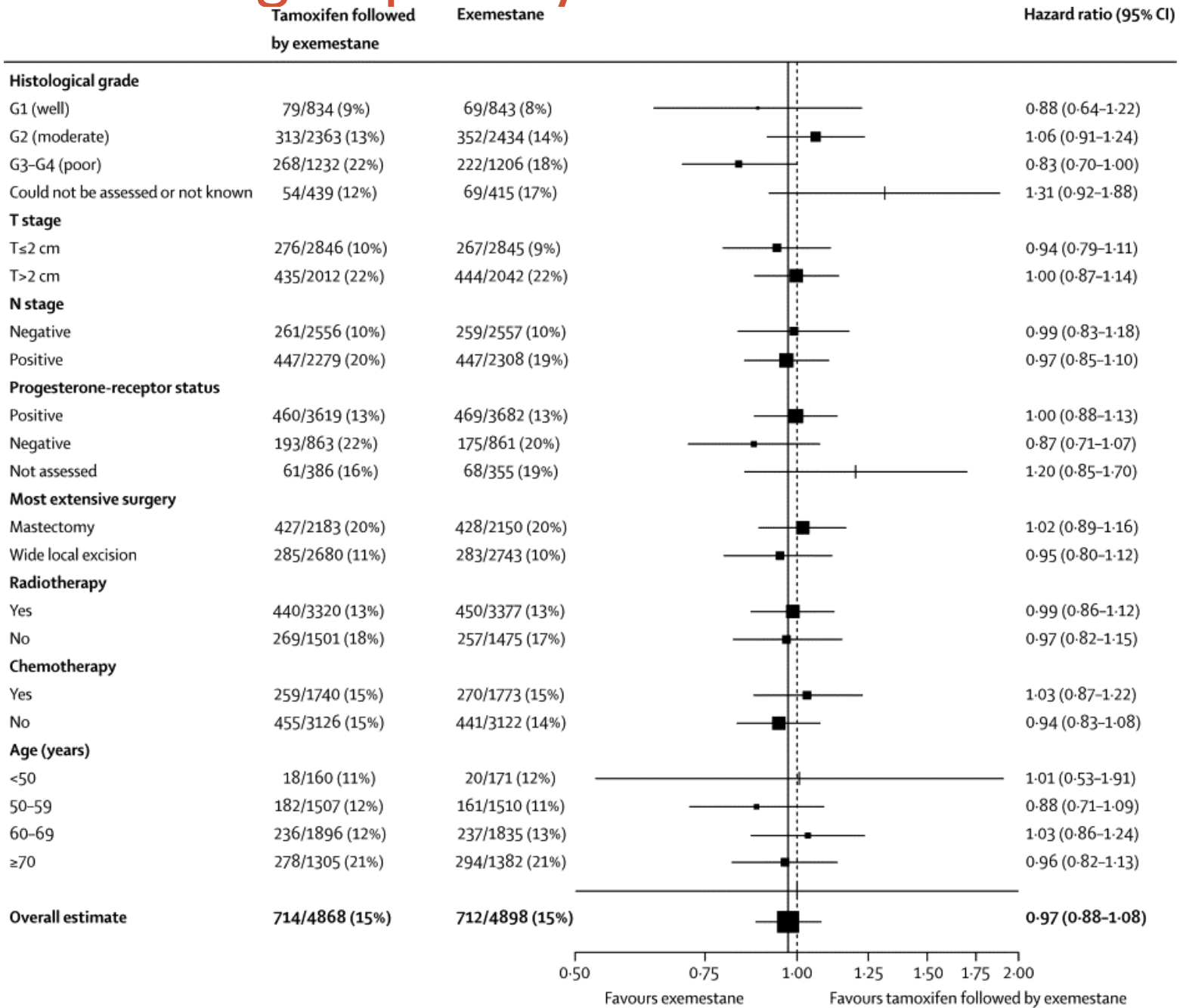
Above: DFS at 5 yrs in ITT population

Left top: Overall survival at 5 yrs in ITT population

Left bottom: Cumulative incidence of relapse at 5 yrs in ITT population

Lancet 2011;377: 321-31

TEAM: Subgroup analysis of DFS



TEAM study

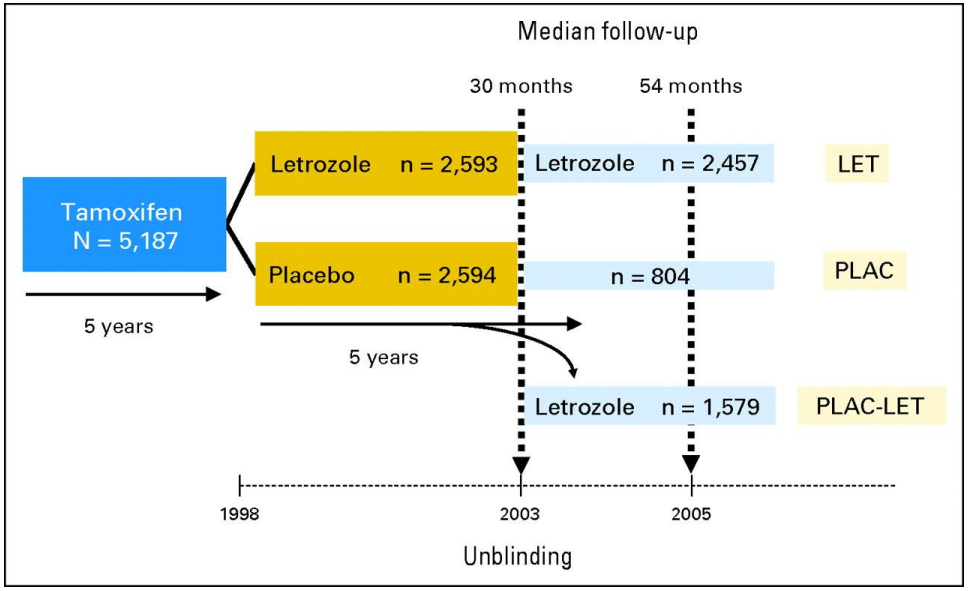
- In the safety analysis, sequential treatment was associated with a higher incidence of gynaecology symptoms, venous thrombosis and endometrial abnormalities than exemestane alone
- Musculoskeletal adverse events, hypertension and hyperlipidaemia were reported more frequently with exemestane alone
- Exemestane alone or after Tam … appropriate options for postmenopausal women

Conclusion

- At 5 yrs, no differences in DFS and OS for exemestane vs. sequential treatment with Tam followed by Exe
- These data were consistent with those from BIG 1-98, in which Tam followed by letrozole or the reverse vs. letrozole monotherapy after median fu of 71 months
- AI x 5 yr and a switch after Tam x 2-3 yrs reduced absolute tumour recurrence rates by 3% vs. Tam monotherapy
- Initial AI associated with a non-significant reduction in mortality, but AI after Tam had a significant reduction in mortality vs. Tam mono

Lancet 2011;377:321-31

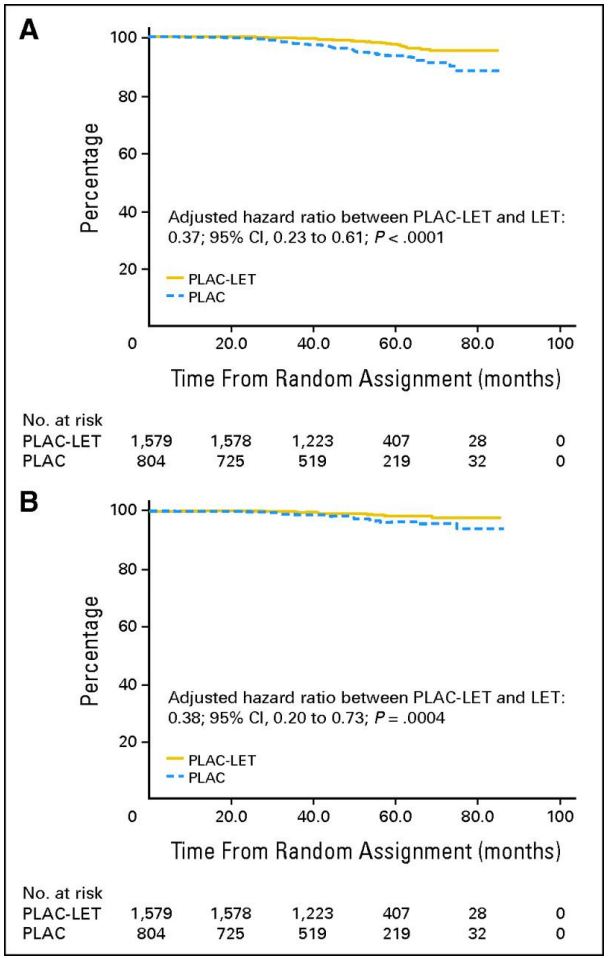
Extended AI – MA.17 trial



- At initial median fu of 2.5 yrs, fewer recurrences or new contralateral BC with extended letrozole (HR 0.58, $p<0.001$)
- No difference in OS, although a survival advantage in the subset of pts with positive axillary LN

PE Goss et al. J Clin Oncol 2008;26:1948-1955

Extended AI – MA.17 trial

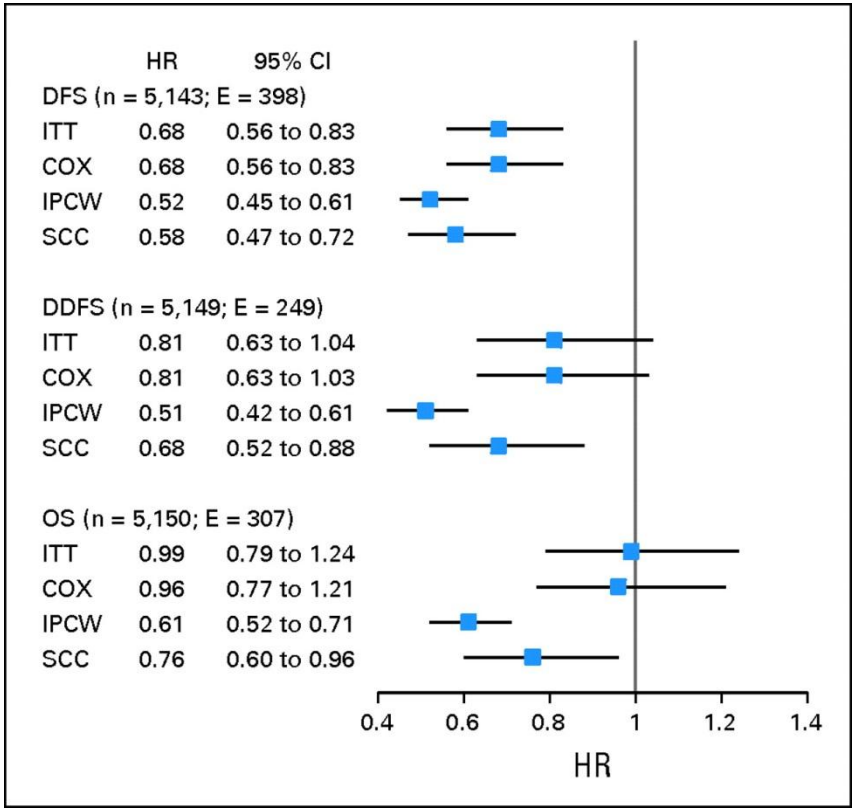


- At a median fu of 5.3 yrs, DFS (HR 0.37, p<0.0001) and distant DFS (HR 0.39, p=0.004) were superior in the plac-let group
- More new osteoporosis and fracture in letrozole group (5.2% vs. 3.1%, p 0.02)
- Providing some evidence for the efficacy of letrozole after no endocrine therapy for an extended period (median time since completion of tamoxifen was 2,8 yrs)

(A) disease-free survival and (B) distant disease free survival; both are calculated from the time of original random assignment

PE Goss et al. J Clin Oncol 2008;26:1948-1955

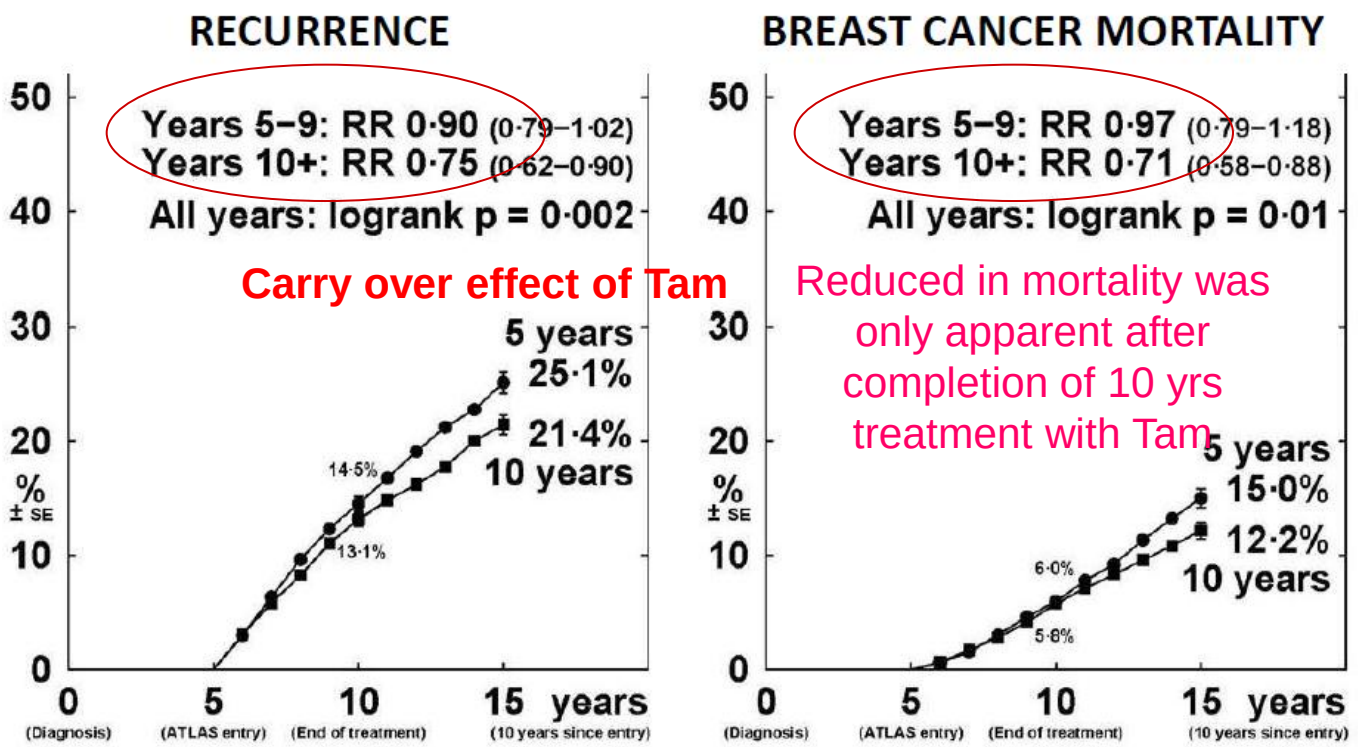
MA.17 – adjusting for crossover



- HR 0.52, p=0.001 for DFS
- HR 0.51, p=0.001 for distant DFS
- HR 0.61, p=0.001 for OS
- Exploratory analyses based on longer follow-up and adjusting for treatment crossover suggest that extended adjuvant letrozole was superior to placebo in DFS, DDFS, and OS

H Jin et al. J Clin Oncol 2011;30:718-721

ATLAS: 6846 women, ER+, 10 vs 5 years tamoxifen



617 vs 711

Recurrence rates (%/year) and logrank analyses			
Tamoxifen allocation	Years 5 – 9	Years 10 – 14	Year 15+
Continue to 10 years	2·83 (428 / 15115)	1·96 (165 / 8439)	2·54 (24 / 945)
Stop at 5 years	3·16 (471 / 14889)	2·66 (214 / 8038)	3·03 (26 / 859)
Rate ratio, from (O−E) / V	0·90 SE 0·06 −24·8 / 224·7	0·74 SE 0·09 −29·1 / 94·7	0·85 SE 0·26 −2·1 / 12·5

331 vs 397

Death rates (%/year total rate − rate in women without recurrence) & logrank analyses			
Tamoxifen allocation	Years 5 – 9	Years 10 – 14	Year 15+
Continue to 10 years	1·17 SE 0·09	1·38 SE 0·12	1·64 SE 0·39
Stop at 5 years	1·21 SE 0·09	2·01 SE 0·15	2·29 SE 0·47
Rate ratio, from (O−E) / V	0·97 SE 0·10 −3·2 / 94·0	0·70 SE 0·10 −27·2 / 77·5	0·79 SE 0·27 −2·5 / 10·6

Tam for a total of 10 years vs. stopping Tam after 5 yrs had little further effect on recurrence rates and death rates between 5 to 9 years after diagnosis. However, during the second decade after diagnosis, women allocated to continue Tam had a 25% lower recurrence rate and a 29% lower BC mortality rate than the women who had been allocated to stop after only 5 yrs

Lancet 2013;381:805-16

Contemporaneous benefit of 10 yr tam: 39% reduction in risk of relapse and 36% risk reduction in BC mortality. After completion of 10 yr, risk reduced by 30% for relapse and 48% for mortality

ER+ disease: Effects of tamoxifen duration on event rate ratio (RR), by time since diagnosis

	5 years tam. vs none: EBCTCG meta-analysis (n=10 645)	10 years tam. vs 5: ATLAS trial (n=6846)	10 years tam. vs none: estimated effects (product of two RRs)
Recurrence in:			
- years 0-4	RR=0.53‡ (0.48-0.57)	(1.0)	RR=0.53‡ (0.48-0.57)
- years 5-9	0.68‡ (0.60-0.78)	0.90 (0.79-1.02)	0.61‡ (0.51-0.73)
- years 10+	0.94 (0.79-1.12)	0.75* (0.62-0.90)	0.70* (0.54-0.91)
Breast cancer mortality in:			
- years 0-4	0.71‡ (0.62-0.80)	(1.0)	0.71‡ (0.62-0.81)
- years 5-9	0.66‡ (0.58-0.75)	0.97 (0.79-1.18)	0.64† (0.50-0.82)
- years 10+	0.73† (0.62-0.86)	0.71§ (0.58-0.88)	0.52‡ (0.40-0.68)
‡2p<0.00001	† 2p=0.0001	§ 2p=0.0016	* 2p<0.01

Same as Lancet 2013;381:805-16

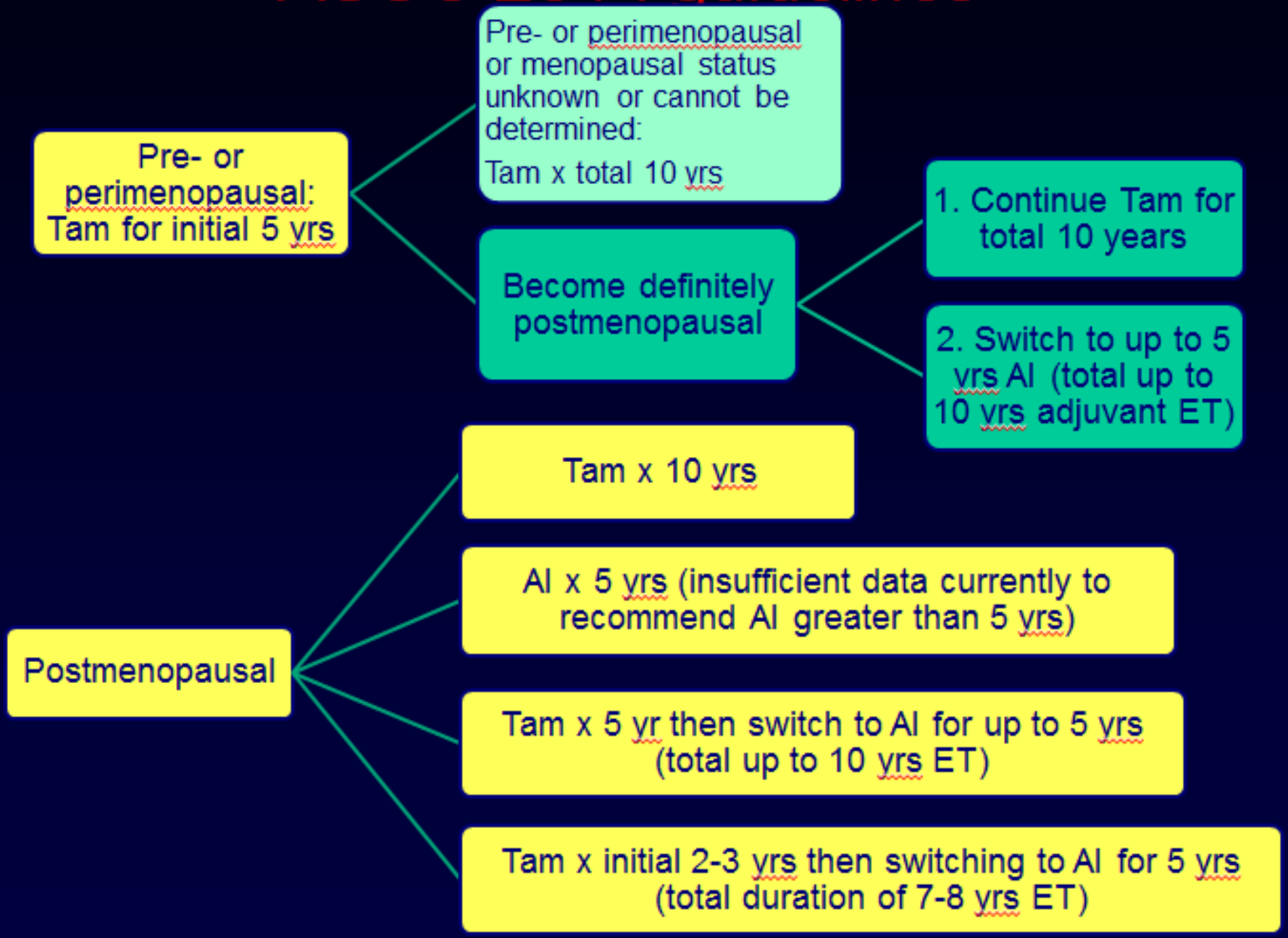
Conclusion from TEXT and SOFT

At 5 years	Combined TEXT and SOFT Analysis		SOFT	
	AI + OFS	TMX + OFS	TMX + OFS	TMX
DFS	91%	87%	86.6%	84.7%
Absolute risk reduction	4%		1.9%	
HR, 95% CI	0.72 (0.60 – 0.85), P <0.001		0.83 (0.66 – 1.04)	
OS	96%	97%	96.7%	95.1%
Absolute risk reduction	1%		1.6%	
HR	1.14 (0.86 – 1.51)		0.74 (0.51 – 1.09)	
Freedom from BC	92.8%	88.8%	88.4%	86.4%
HR	0.66 (0.55 – 0.80), P<0.001		0.81 (0.63 – 1.03), P=0.09	
Freedom from BC distant recurrence	93.8%	92%		
HR	0.78 (0.62 – 0.97), P=0.02		0.88 (0.66 – 1.18), P=0.4	

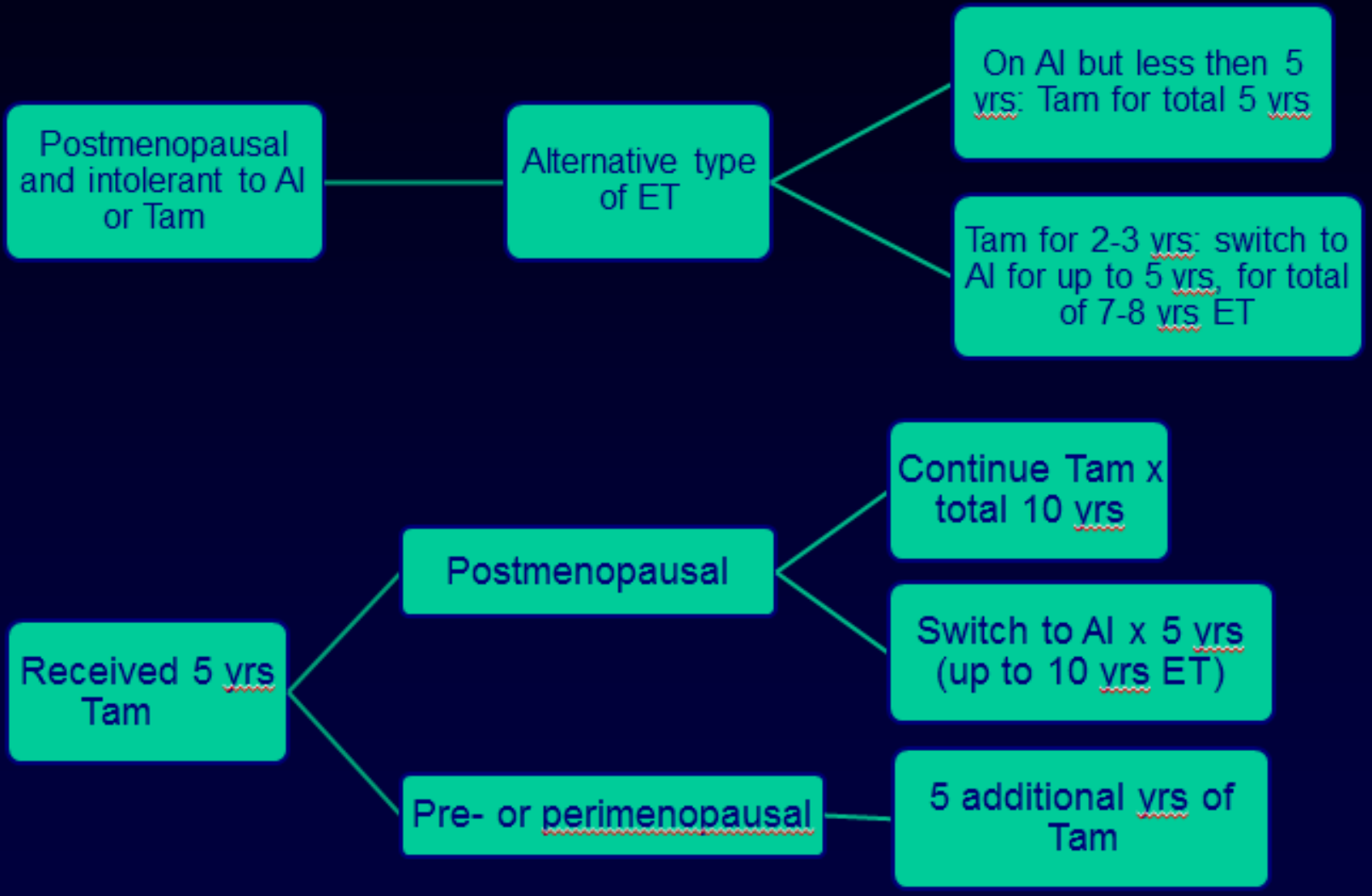
SOFT trial: Freedom from BC HR 0.78 (0.6 – 1.02) and freedom from BC distant recurrence HR 0.87 (0.64 – 1.17) for patients on prior chemotherapy

In a large subset of women with higher-risk cancers, nearly all of whom received chemo but remained premenopausal, ovarian suppression added to TMX reduced risk of BC recurrence

ASCO 2014 guidelines



ASCO 2014 guidelines



Key changes: Tam is now recommended for a duration of up to 10 years rather than 5 years

ASCO 2016 guidelines on ovarian suppression

The bottom line
Guideline question
1. Should premenopausal women with ER+ tumours receive adjuvant ovarian suppression in addition to standard adjuvant therapy, if so, in which subsets of patients? 2. If ovarian suppression is recommended, should ovarian suppression be administered in combination with TMX or an AI?
Target population: premenopausal women with stage I to III HR+ BC
Recommendations 1 (see next 1 slide)
Benefits: increasing DFS, freedom from BC, and freedom from distance recurrence
Harms: worse menopausal symptoms and sexual functioning, including hot flashes, sweating, weight gain, vaginal dryness and decreased libido
Recommendation 2 (see next 2 slide)
Benefits: same as above
Harms: worse menopausal symptoms and sexual functioning, including hot flashes, sweating, weight gain, vagina dryness, and decreased libido; osteopenia/osteoporosis

J Clin Oncol March 2016: Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression

ASCO 2016 guidelines on ovarian suppression

Table 5. Clinical Question 1 Recommendations.

Recommendation 1.1

The Panel recommends that higher-risk patients should receive ovarian suppression in addition to adjuvant endocrine therapy, whereas lower-risk patients should not.

Recommendation type: Evidence-based and Panel consensus; benefits outweigh harms; Evidence quality: Intermediate; Strength of Recommendation: Moderate

Qualifying statement:

The Panel notes that two prospective studies did not show overall clinical benefit for the addition of ovarian suppression to tamoxifen in premenopausal, ER-positive breast cancer. However, in a large subset of women with higher-risk cancers, nearly all of whom received chemotherapy but remained premenopausal, ovarian suppression added to tamoxifen reduced the risk of breast cancer recurrence. Because of the design of the clinical trials, there are few definitive criteria by which to define risk.

Recommendation 1.2

Women with stage II or stage III breast cancers who would ordinarily be advised to receive adjuvant chemotherapy should receive ovarian suppression in addition to endocrine therapy.

Recommendation type: Evidence-based and Panel consensus; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Moderate

Recommendation 1.3

Women with stage I or II breast cancers at higher risk of recurrence, who might consider chemotherapy, may also be offered ovarian suppression in addition to endocrine therapy.

Recommendation type: Evidence-based and Panel consensus; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Moderate

Recommendation 1.4

Women with stage I breast cancers not warranting chemotherapy should receive endocrine therapy but not receive ovarian suppression.

Recommendation type: Evidence-based; harms outweigh benefits; Evidence quality: High; Strength of Recommendation: Strong

Recommendation 1.5

Women with node-negative cancers 1 cm or less (T1a, T1b) should receive endocrine therapy but not receive ovarian suppression.

Recommendation type: Evidence-based; harms outweigh benefits; Evidence quality: High; Strength of Recommendation: Strong

Qualifying statements:

The standard duration of ovarian suppression in the included trials was 5 years. With no comparative data available on alternative durations, the Panel supports ovarian suppression for 5 years.

To date there is no adequate evidence for assessing the benefit of adjuvant ovarian suppression *in women at sufficient risk to warrant chemotherapy compared with 10 years of tamoxifen.*

There is no current role for ovarian suppression as adjuvant therapy in ER-negative breast cancers.

There are substantial adverse effects to ovarian suppression. Clinicians and patients should consider the tradeoffs of adverse effects when choosing ovarian suppression.

The long-term effects of ovarian suppression on breast cancer risk and survival are not yet established.

Abbreviation: ER, estrogen receptor.

Adjuvant ET for premenopausal – St Gallen 2015

Endocrine Therapy
Premenopausal: 'Typical' Cases

Age 42, node negative, grade 2, T1, no chemotherapy:

1. Tam alone 85%
2. OFS plus Tam 12.5%
3. OFS plus AI 0
4. None of the above 2.5%
9. Abstain 0

Age 34, node positive, grade 3, T1, remaining premenopausal after adjuvant chemotherapy:

1. Tam alone 2.3%
2. OFS plus Tam 23.3%
3. OFS plus exemestane 69.8%
4. None of the above 2.3%
9. Abstain 2.3%

Endocrine Therapy
Premenopausal: Selection Factors

Factors arguing for use of OFS + AI rather than OFS + tamoxifen are:

- Age <= 35 years 59.4/37.5/3.1 1Y/ 2N/ 9A
- Premenopausal oestrogen level after adjuvant chemotherapy 43.9/51.2/4.9 1Y/ 2N/ 9A
- Grade 3 57.1/35.7/7.1 1Y/ 2N/ 9A
- Involvement of 4 or more nodes 92.5/5/2.5% 1Y/ 2N/ 9A
- Adverse result of multi-gene test 65.8/31.6/2.6% 1Y/ 2N/ 9A

Endocrine Therapy
Premenopausal: Selection Factors

Factors arguing for including ovarian function suppression (OFS) are:

- Age <= 35 years 81%/19%/0 1Y/ 2N/ 9A
- Premenopausal oestrogen level after adjuvant chemotherapy 73.7/26.3/0 1Y/ 2N/ 9A
- Grade 3 55.9/38.2/0 1Y/ 2N/ 9A
- Involvement of 4 or more nodes 89.7/10.3/0 1Y/ 2N/ 9A
- Adverse result of multi-gene test 60/24.4/15.6% 1Y/ 2N/ 9A

Extra question

- If you decide to give OFS, overall you're more likely to recommend Tam or AI?
- Tamoxifen 36.6%
- AI 58.5%
- Abstain 4.9%

Adjuvant ET for premenopausal – St Gallen 2015

Extra question

Optimal duration of OFS we do not know, yet!

- 2-3 years 16.7%
- 5 years 56.7%
- Lifelong 3.3%
- Abstain 23.3%

Adiuvant hormone – St Gallen 2015

Endocrine Therapy
Postmenopausal

Can some patients be adequately treated with tamoxifen alone? 97.6/2.4/0 1Y/ 2N/ 9A

Factors arguing for inclusion of an AI at some point are:

- Age < 60 31/69/0 1Y/ 2N/ 9A
- Involvement of 4 or more nodes 97.6/2.4/0 1Y/ 2N/ 9A
- Grade 3 or high Ki-67 97.7/2.3/0 1Y/ 2N/ 9A
- HER2 positivity 71.1/28.9/0 1Y/ 2N/ 9A

If an AI is used, should it be started upfront:

- In all patients? 47.5/52.5/0 1Y/ 2N/ 9A
- In patients at higher risk? 95.5/4.5/0 1Y/ 2N/ 9A

Can upfront AI be switched to TAM after 2 yrs? 75/22.5/2.5 1Y/ 2N/ 9A

Endocrine Therapy
Duration

After 5 years of adjuvant Tam, continued *AI, AI/OS or Tam* to 10 years should be recommended to:

- Premenopausal patients with node-positive disease? 100/0/0
- Premenopausal patients with node-negative disease? 15.4/74.4/10.3
- Premenopausal patients with grade 3 or high Ki-67? 73.8/21.4/4.8
- Postmenopausal patients with node-positive disease? 95.2/4.8/0
- Postmenopausal patients with node-negative disease? 14.6/80.5/4.7
- Postmenopausal patients with grade 3 or high Ki-67? 76.7/18.6/4.7
- Postmenopausal patients, premenopausal at baseline? 66.7/25.6/7.2

Endocrine Therapy
Duration

Provided an indication exists for therapy beyond the first 5 years:

After 5 years of adjuvant therapy involving *switch from Tam to an AI* (therefore assuming postmenopausal status at the 5 year time point and reasonable tolerance to endocrine therapy), patients should be recommended to receive:

- A further 5 years of tamoxifen 39.4/57.6/3 1Y/ 2N/ 9A
- Continue AI to a cumulative total of 5 years AI 75/22.5/2.5 1Y/ 2N/ 9A
- A further 5 years AI 31.4/60/8.6 1Y/ 2N/ 9A
- No further endocrine therapy 13.9/83.3/2.8

After 5 years of *straight AI* adjuvant therapy, patients should be recommended to receive:

- A further 3 to 5 years of tamoxifen 34.1/63.4/2.4 1Y/ 2N/ 9A
- A further 3 to 5 years AI 42.9/57.1/0 1Y/ 2N/ 9A
- No further endocrine therapy 40.9/54.5/4.5 1Y/ 2N/ 9A

Extra question

- After 5 years of adjuvant therapy involving tamoxifen x 2 years followed by AI x 3 years (assuming postmenopausal status and tolerance of hormonal therapy), the preferred treatment is: Needs clarification!
- 5 more years of tamoxifen 3.2%
- Continue AI to a total of 5 years 54.8%
- Continue AI for 5 full years 16.1%
- No further treatment 16.1%
- Abstain 9.7

Adjuvant hormone – St Gallen 2015

Extra question

After 5 years of straight AI: We do not (yet) know!

- 3-5 years of tam 27%
- 3-5 years of AI 37.8%
- No further endocrine treatment 29.7%
- Abstain 5.4%

Adjuvant ET – NCCN

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

ADJUVANT ENDOCRINE THERAPY

Premenopausal[1] at diagnosis → Tamoxifen[2,3] for 5 y (category 1) ± ovarian suppression or ablation (category 2B)

- Postmenopausal[1] → Aromatase inhibitor for 5 y[4] (category 1) or Consider tamoxifen[2] for an additional 5 y to complete 10 y
- Premenopausal[1] → Consider tamoxifen[2] for an additional 5 y to complete 10 y or No further endocrine therapy

Postmenopausal[1] at diagnosis

- Aromatase inhibitor[4] for 5 y (category 1) or Tamoxifen[2] for 2–3 y or Aromatase inhibitor[4] for 2–3 y (category 1) → Aromatase inhibitor to complete 5 y[4] of endocrine therapy (category 1) or Up to 5 y of an aromatase inhibitor[4] (category 2B); Tamoxifen[2] to complete 5 y of endocrine therapy (category 1)
- Tamoxifen[2] for 4.5–6 y → Aromatase inhibitor for 5 y[4] (category 1) or Consider tamoxifen[2] for an additional 5 y to complete 10 y
- Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors → Tamoxifen[2] for 5 y (category 1) or Consider tamoxifen[2] for up to 10 y

[1]See Definition of Menopause (BINV-L).
[2]Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.
[3]Aromatase inhibitor for 5 y + ovarian suppression may be considered as an alternative option based on SOFT and TEXT clinical trial outcomes. Pagani O, Regan M, Walley B, et al. Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2014; 371:107-118.
[4]The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and neoadjuvant settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

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ADJUVANT ENDOCRINE THERAPY

Premenopausal[1] at diagnosis → Tamoxifen for 5 y (category 1) ± ovarian suppression or ablation (category 1)[2] or Aromatase inhibitor for 5 y + ovarian suppression or ablation (category 1)[2]

- Postmenopausal[1] → Aromatase inhibitor for 5 y[3] (category 1) or Consider tamoxifen[4] for an additional 5 y to complete 10 y
- Premenopausal[1] → Consider tamoxifen[4] for an additional 5 y to complete 10 y or No further endocrine therapy

Postmenopausal[1] at diagnosis

- Aromatase inhibitor[3] for 5 y (category 1) or Tamoxifen[4] for 2–3 y or Aromatase inhibitor[3] for 2–3 y (category 1) → Aromatase inhibitor to complete 5 y[3] of endocrine therapy (category 1) or Up to 5 y of an aromatase inhibitor[3] (category 2B); Tamoxifen[4] to complete 5 y of endocrine therapy (category 1)
- Tamoxifen[4] for 4.5–6 y → Aromatase inhibitor for 5 y[3] (category 1) or Consider tamoxifen[4] for an additional 5 y to complete 10 y
- Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors → Tamoxifen[4] for 5 y (category 1) or Consider tamoxifen[4] for up to 10 y

[1]See Definition of Menopause (BINV-M).
[2]Aromatase inhibitor or tamoxifen for 5 y plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal women at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement, Pagani, NEJM 2014, Prudence, NEJM 2014).Survival data still pending.
[3]The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and preoperative settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.
[4]Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 gene testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.

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BINV-J

Side effects of tamoxifen

Average annual rate per 1000 women

Type of events	Placebo	Tamoxifen	Risk ratio
Endometrial cancer	0.91	2.30	2.53
≤ 49	1.09	1.32	1.21
≥ 50	0.76	3.05	4.01
Ischaemic heart disease	2.37	2.73	1.15
Stroke	0.92	1.45	1.59
Transient ischaemic attack	0.96	0.73	0.76
Pulmonary embolism	0.23	0.69	3.01
DVT	0.84	1.34	1.6
Cataract	21.72	24.82	1.14

Hot flashes, vaginal discharge, depression

All endometrial cancers in the tamoxifen group were stage I (localized disease); no endometrial cancer deaths have occurred in this group. No liver cancers or increase in colon, rectal, ovarian, or other tumors was observed in the tamoxifen group

Incidence of uterus (not cervix) Ca
ER+ disease, ~ 5-yr Tam

		incidence (%)	Loss (%)
Entry age < 45	Tam	(10 yr) 0.4	0.1 (se 0.3) 2p=0.97
	Control	0.3	
45 - 54	Tam	(10 yr) 0.9	0.1 (se 0.4) 2p=0.17
	Control	0.8	
55 - 69	Tam	(15-yr) 3.8	2.6 (se 0.6) 2p<0.00001
	Control	1.1	
70+	Tam	(5- yr) 0	0 (se 0.0) 2p =0.11
	Control	0	

Tam ↑ uterine Ca incidence (excl cervix) RR 2.4 (se 0.32), p=0.00002). Risk is strongly correlated with age, with little absolute risk for entry age < 45 or 45-54, but for 55-69 yr, 15-yr incidence was 3.8% in Tam group vs. 1.1% in control group, absolute increase 2.6% ([se 0.6], 95% CI 1.4-3.8)

EBCTCG. Lancet 2011; 378: 771–84

Adverse events of Tam

Death without recurrence	No. of events (both groups)	Event RR	P value
Stroke	64	1.37	0.27
Pulmonary embolus	12	2.30	0.25
Heart and other vascular	212	0.89	0.43
Uterus, excluding cervix	10	4.28	0.07
Other, non-breast	187	1.00	1.00

Uterus, excl cervix incidence, by age at entry (yr)	No. of events (both groups)	Event RR	P value
< 45	11	1.04	1.00
45 - 54	25	1.75	0.25
55 - 69	71	2.96	0.00002
≥ 70	1	-	-
All ages	108	2.4	0.00002

Side effects of AIs

↑ cardiovascular disease*	OR = 1.26, 95% CI = 1.10 to 1.43, P < .001
↑ bone fractures	OR = 1.47, 95% CI = 1.34 to 1.61, P < .001
↓ venous thrombosis	OR = 0.55, 95% CI = 0.46 to 0.64, P < .001
↓ endometrial carcinoma	OR = 0.34, 95% CI = 0.22 to 0.53, P < .001

Five years of aromatase inhibitors was associated with a non-statistically significant increased odds of death without recurrence compared with 5 years of tamoxifen alone or tamoxifen for 2-3 years followed by an aromatase inhibitor for 2-3 years (OR = 1.11, 95% CI = 0.98 to 1.26, P = .09)
***Risk of heart attack, angina, heart failure, and hypercholesterolemia**

The cumulative toxicity of aromatase inhibitors when used as up-front treatment may explain the lack of overall survival benefit despite improvements in disease-free survival. Switching from tamoxifen to aromatase inhibitors reduces this toxicity and is likely the best balance between efficacy and toxicity

J Natl Cancer Inst 2011; 103(17):1299–1309

AI vs. Tamoxifen – Averse events on treatment or within 14 days of discontinuation

	Anastrozole n=3,092 (%)	Tamoxifen n=3,094 (%)	p-value
潮熱 (hot flushes)	1104 (35.7)	1264 (40.9)	<0.0001
關節疼痛	1100 (35.6)	911 (29.4)	<0.0001
陰道出血	167 (5.4)	317 (10.2)	<0.0001
陰道分泌增加	109 (3.5)	408 (13.2)	<0.0001
子宮癌	5 (0.2)	17 (0.8)	0.02
骨折	340 (11)	237 (7.7)	<0.0001
缺血性心臟病ischaemic cardiovascular disease	127 (4.1)	104 (3.4)	0.1
缺血性中風ischaemic cerebrovascular disease	62 (2)	88 (2.8)	0.03
栓塞事件Venous thrombo-embolic events	87 (2.8)	140 (4.5)	0.0004
靜脈栓塞Deep venous thrombo-embolic events	48 (1.6)	74 (2.4)	0.02

ATAC Trialists' Group Lancet 2005;365:60-62

ATAC – Safety of long term AI

	Anastrozole n=3,092 (%)	Tamoxifen n=3,094 (%)
All cancers	425 (13.7)	431 (13.9)
Endometrial cancer	6 (0.2)	24 (0.8)
Lung	51 (1·6)	34 (1·1)
All gastrointestinal	104 (3·4)	72 (2.3)
Colorectal	66 (2·1)	44 (1.4)
Gastric	12 (0.4)	8 (0.3)
Melanoma	8 (0·3)	19 (0·6)

Lancet Oncol. 2010 Dec;11(12):1135-41

ATAC update

- During treatment, women in the anastrozole group had fewer serious adverse events related to treatment than women in the tamoxifen group. After treatment was completed, however, rates of serious adverse events evened out between the two groups. Patients taking anastrozole reported more fractures during treatment than those taking tamoxifen, but after the completion of treatment fracture rates again became similar in both groups
- Patients taking tamoxifen had higher rates of endometrial cancer and melanoma than those taking anastrozole. There was a slight trend toward more colorectal and lung cancers in patients taking anastrozole compared with those taking tamoxifen. Overall, however, cancers other than breast cancer occurred at similar rates in both groups

Lancet Oncol. 2010 Dec;11(12):1135-41

Adverse events reported post-treatment – IES updates

	Exemestane, n=2,105		Tamoxifen, n=2,036			
Adverse event	No.	%	No.	%	Odds ratio	P
All cardiovascular events (excluding HT and VTE)	259	12.3	211	10.4	1.21	0.049
Ischaemic cardiovascular disease	127	6	94	4.6	1.33	0.043
Angina	110	5.2	79	3.9	1.37	0.038
Hypertension (HT)	563	26.7	475	23.3	1.20	0.011
VTE (Venous thromboembolic event)	20	1	19	0.9	1.02	0.955
DTV (deep vein thrombosis)	17	0.8	18	0.9	0.91	0.788

Denominators include patients who are disease free and have at least 6 months post-treatment follow up

JM Bliss, et al. J Clin Oncol 2011;30:709-717

Adverse events of AI

- Focusing on AEs after treatment cessation, musculoskeletal pain, arthritis, and osteoporosis became less frequent
- No significant differences between treatments were observed for any individual type of AE
- Improvement as time since discontinuation of therapy increases
- Differences in fracture risk between treatment groups is no longer evident, and other AEs are regressing
- Larger no. of patients who switched reported cardiovascular events, but not translate into increased vascular death rate

JM Bliss, et al. J Clin Oncol 2011;30:709-717

Early vs. premature vs. induced menopause

- Menopause is the point at which a woman stops menstruating
- While the average age of menopause in the United States is 51, the usual range is from 45 to 55. If you completely stop having periods before the age of 45, it is called an early menopause. If you stop menstruating even earlier -- before the age of 40 -- it is called premature menopause
- Induced: Menopause induced by an unusual event, such as occurs when the ovaries are damaged by radiation, chemotherapy or other medications; or as occurs when the ovaries are surgically removed (by bilateral oophorectomy)

Definition of menopause

- Any of the followings:
  - Prior bilateral oophorectomy
  - Age $\geq$ 60 yr
  - Age < 60 y and amenorrhoeic for 12 or more months in the absence of chemo, Tam, toremifene, or ovarian suppression and FSH and estradiol in the postmenopausal range
  - If taking Tam or toremifene, and age < 60 y, then FSH and plasma estradiol level in postmenopausal ranges

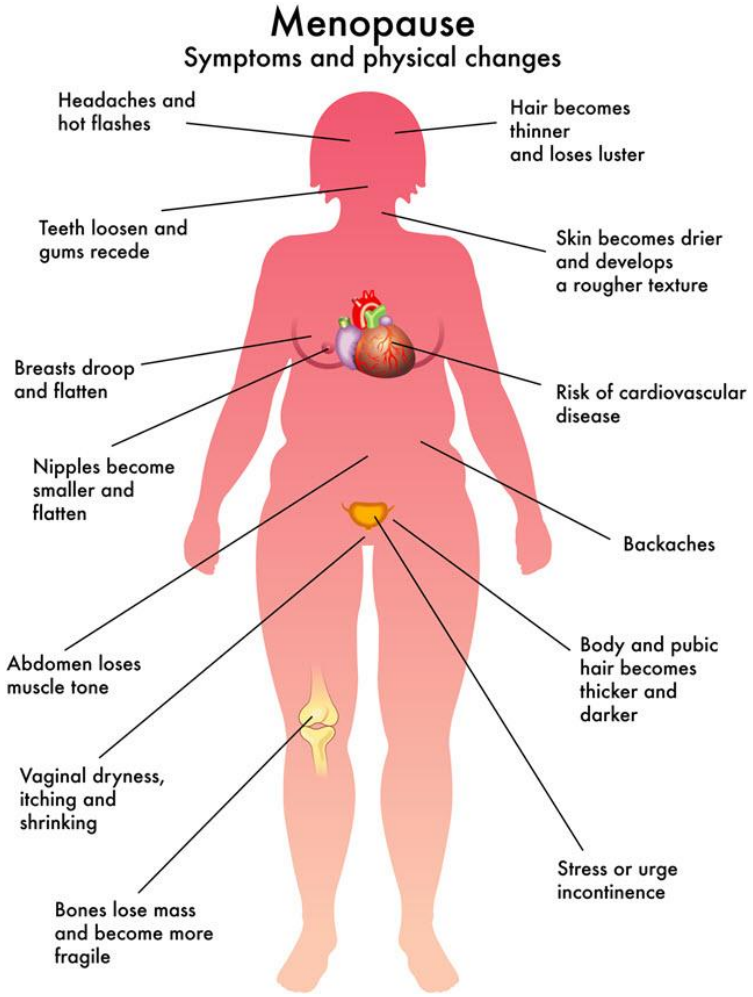
NCCN

Diagnosis of menopause

- When estradiol levels are below 30, it may signal that you are in menopause
- FSH causes your ovaries to produce estrogen. When your ovaries slow down their production of estrogen, your levels of FSH increase. When your FSH levels rise above 40 mIU/mL, it usually indicates that you are in menopause

Symptoms of menopause

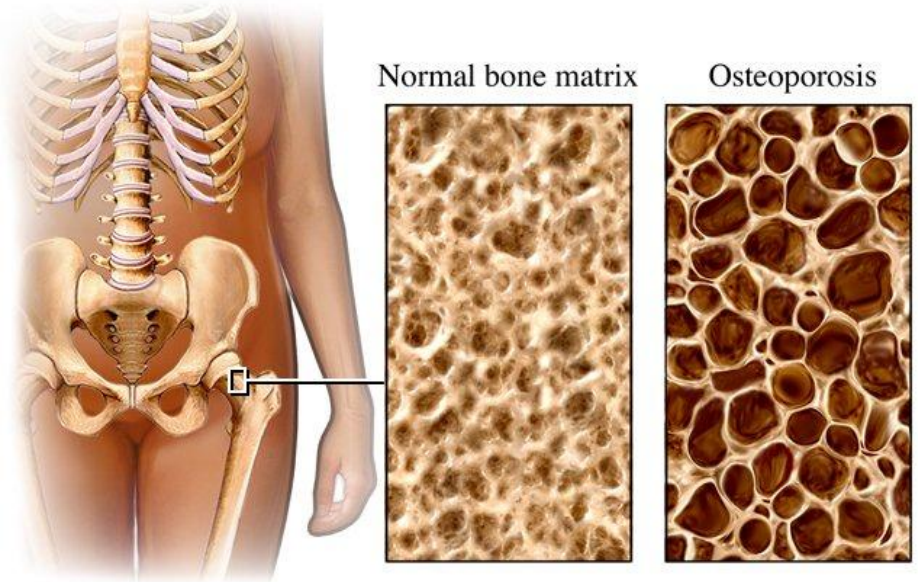
- Hot flashes and night sweats
- Mood swings
- Headaches
- Insomnia
- Vaginal dryness, urinary problem (incontinence, prone to infection)
- Weight gain
- Memory and cognitive changes
- Fatique
- Decreased libido
- Dizziness
- Aching joints and muscles
- Hair loss

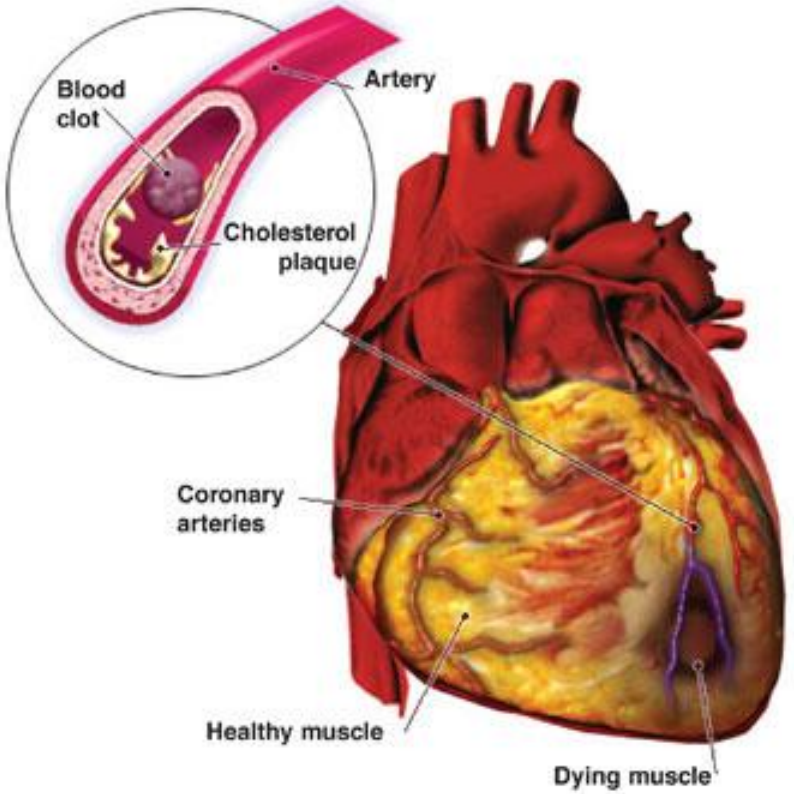


…35 Symptoms of Menopause

Complication of premature menopause

- Osteoporosis
  - A skeletal disorder characterized by bone fragility. The reduction in bone mass and bone porosity
- Cardiovascular disease





Relationship hormonal therapy with lipid metabolism and heart disease

- Tamoxifen and toremifene inhibit the conversion of delta 8-cholestenol to lathosterol so that serum total and LDL cholesterol levels are lowered by downregulation of cholesterol synthesis
- Reduced risk of coronary artery disease will probably occur also during long term toremifene treatment because of the drug reduces cholesterol and its synthesis, similar to tamoxifen

Nonestrogen treatment modalities for vasomotor symptoms associated with menopause

- Shown to be safe and effective in short term use include
  - Black cohosh黑升麻
  - Exercise
  - Gabapentin
  - Medroxyprogesterone acetate
  - SSRIs (e.g. paroxetine)
  - Soy protein
  - Megestrol acetate
  - Venlafaxine

SE Fugate, et al. Ann Pharmacother. 2004 Sep;38(9):1482-99

Treatment of menopause-associated vasomotor symptoms

- Lifestyle changes, e.g. keep core body temp cool, paced respiration
- Dietary isoflavones大豆異黃酮, black cohosh, vit E
  - Clinical trial results insufficient
  - No serious side effects with short-term use
- Nonhormonal agents
  - Venlafaxine速悅
  - Paroxetine, fluoxetine
  - Gabapentin加巴噴丁

Position statement of The North American Menopause Society. Menopause. 2004 Jan-Feb;11(1):11-33

Treatment for menopausal symptoms in BC patients

- The use of estrogen, progesterone, or SERMs to treat osteoporosis or osteopenia in women with BC is discouraged (NCCN)
- The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density
- Optimal duration of bisphosphonate therapy has not been established

Assessment of bone loss

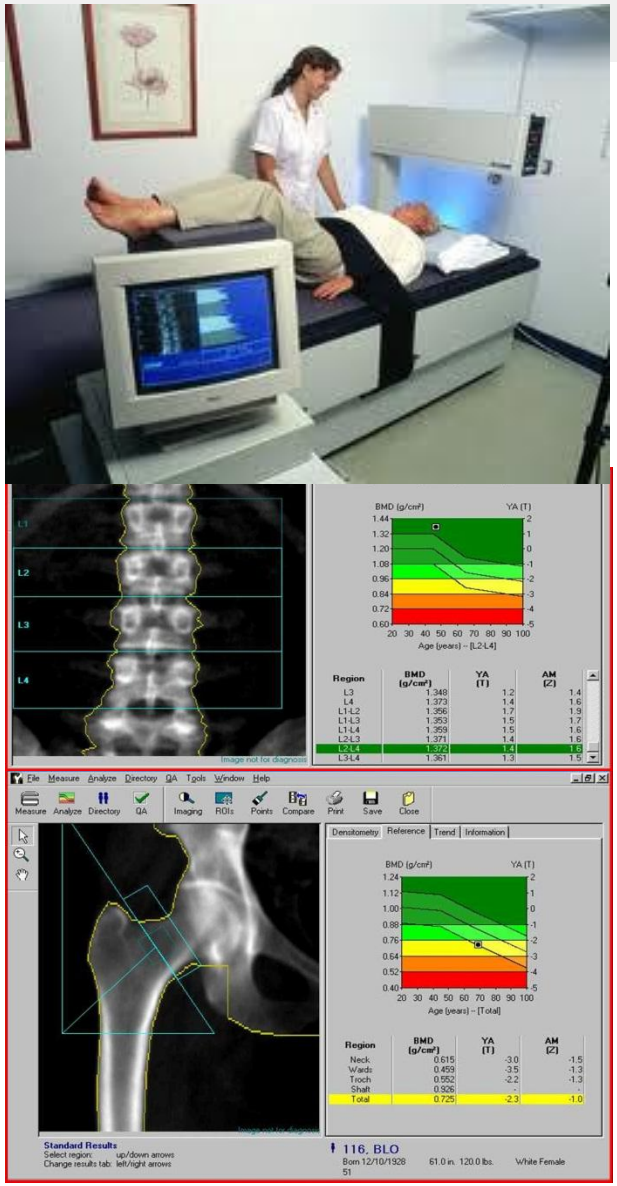
- In terms of BMD, osteoporosis is defined by WHO as a BMD that is 2.5 SD or more below the average value for young healthy women (a T-score of < -2.5SD)
- Breast cancer treatment associated with premature ovarian suppression and hence increased risk of osteoporosis:
  - LHRHa
  - Chemotherapy
  - Surgical ablation
- Adjuvant breast cancer treatment associated with bone loss:
  - Tamoxifen
  - AIs

Tamoxifen: effect on bone health

- Tamoxifen is an estrogen antagonist
- With respect to bone, Tam has a different effect in pre and postmenopausal women
- In premenopausal with high levels of circulating estrogen from ovaries, Tam predominantly has an anti-estrogenic effect causing increased loss of BMD for 1-2 yrs, about 1-2% and is not persistent through 5 yrs of Tam
- In postmenopausal in low estrogen states, Tam has an estrogen agonist effect causing a small but significant increase in BMD, lead to a significant reduction in risk of fractures

(UK expert group consensus position statement 2008)

骨質密度(BMD)檢查 – DEXA scan



- Dual Energy Xray Absorptionmetry
- Means of measuring bone mineral density (BMD)
- Can detect changes after about a 1% change
- A DEXA scan lasts about 10 minutes, and exposes the patient to less radiation than a standard chest x-ray
- Typically used to diagnose and follow osteoporosis

Understand DEXA scan results

- T score
  - Compares your bone density to the optimal peak bone density for your gender
  - It is reported as number of standard deviations below the average
  - T-score of > -1 is considered normal
  - T-score of -1 to -2.5 is considered osteopenia, and a risk for developing osteoporosis
  - A T-score of < -2.5 is diagnostic of osteoporosis
- Z score
  - Compare your results to others of your same age, weight, ethnicity, and gender (age-matched comparison)
  - This is useful to determine if there is something unusual contributing to your bone loss
  - A Z-score of < -1.5 raises concern of factors other than aging as contributing to osteoporosis. These factors may include thyroid abnormalities, malnutrition, medication interactions, tobacco use, and others

Assessment and treatment of bone loss – NICE guideline

- Pts with early invasive breast cancer should have a baseline DEXA scan to assess BMD if they
  - Are starting adjuvant AI
  - Have treatment-induced menopause
  - Are starting ovarian ablation/suppression therapy
- Do not offer a DEXA scan who are receiving Tam alone, regardless of pretreatment menopausal status
- Offer bisphosphonates identified by algorithms 1 and 2

Algorithm 1: Women experience premature menopause

- Development of a treatment-induced menopause or planned ovarian suppression treatment before age of 45 yrs are indications for evaluation of BMD by DAX
- No requirement to obtain a DAX before starting treatment but a baseline within 3 months of commencing OS and within 12 months of developing postchemo amenorrhoea

Algorithm 2: Postmenopausal women

- Use of an AI is an indication of DXA
- Baseline within 3 months of commencing
- Monitoring and treatment depends on baseline BMD, age, and presence of any major risk factors for osteoporotic fracture:
  - Previous fragility fracture > age of 50 yrs
  - Parental Hx of fracture
  - BMI < 22
  - Alcohol consumption of $\geq$ 4 units/day
  - Diseases known to increase fracture risk such as premature menopause, RA
  - Ankylosing spondylitis, immobility, Crohn's disease
  - Prior oral steroid use for > 6months

Recommendations according to risk group

- High risk
  - Baseline T-score < -2
  - Assess for other causes of osteoporosis
  - Bisphosphonate in addition of lifestyle advice, Ca and vit D supplementation
- Medium risk
  - T-score between –1 and –2
  - Lifestyle advice plus Ca 1g/day and vit D 400-800IU*
  - FU DEXA scan in 24 months
- Low risk
  - Normal BMD (T-score > -1)
  - Lifestyle advice (diet, weight-bearing exercise, reduce alcohol consumption and cessation of smoking)
  - No FU BMD required unless clinically indicated

*** Unless dietary intake of Ca >1g/day and serum 25-hydroxyvitamin D > 20 μg/L**

UK expert group 2008 recommendation for bisphosphonate

- Elderly (> 75 yrs of age) women with one or more risk factors for osteoporotic fracture irrespective of BMD
- Postmenopausal: T score < -2.0
- Women with premature menopause: T score < -2.0, with exception of those receiving ovarian suppression plus an AI in whom the recommended T-score for intervention is (<) –1, due to very rapid losses of bone occurs in this group

Bisphosphonate therapy 雙磷酸鹽類藥物

- Weekly oral alendronate 70mg or risedronate 35mg
- Monthly oral ibandronate 150mg
- 3-monthly iv ibandronate 3mg
- 6-monthly iv zoledronic acid 4mg
- Contraindicated if CrCl < 30ml/min/1.73m^2 or hypocalcaemia
- Oral bisphosphonates must be used with caution in pts with esophageal disease, although iv will be appropriate in such pts
- FU with a repeat DEXA after 24 months and/or measurement of a bone resorption marker

Assessment and treatment of osteoporosis and osteopenia in post-menopausal women who are about to begin AI

- Baseline BMD – dual energy x-ray absorptiometry (DEXA) of hip and spine
  - T score < -2.5: begin Ca and vit D, and begin therapy with bisphosphonate; repeat BMD annually
  - T score between -1.0 and -2.5: begin Ca and vit D; repeat BMD annually
  - T score> -1: reassure; begin Ca and vit D; repeat BMD annually (ASCO 2003 Recommendations)
- Vit D and Ca levels should be obtained prior to initiating bisphosphonate therapy
- RFT should be monitored prior to initiation of bisphosphonate therapy

Cost-effectiveness of fracture prevention in postmenopausal women who receive aromatase inhibitors for early breast cancer

- The following strategies were compared
  - No intervention
  - One-time bone mineral density (BMD) screening and selective bisphosphonate therapy in women with osteoporosis or osteopenia
  - Annual BMD screening and selective bisphosphonate therapy in women with osteoporosis or osteopenia
  - Universal bisphosphonate therapy
- Outcomes were quality-adjusted life-years (QALYs), lifetime cost, and incremental cost-effectiveness ratio (ICER)

K Ito, et al. J Clin Oncol 2012;30:1468-1475

Results

- ICERs for annual BMD screening followed by oral bisphosphonates for those with osteoporosis, annual BMD screening followed by oral bisphosphonates for those with osteopenia, and universal treatment with oral bisphosphonates were $87,300, $129,300, and $283,600 per QALY gained, respectively
- One-time BMD screening followed by oral bisphosphonates for those with osteoporosis or osteopenia was dominated
- In postmenopausal women receiving adjuvant AIs for HR-positive EBC, a policy of baseline and annual BMD screening followed by selective treatment with oral bisphosphonates for those diagnosed with osteoporosis is a cost-effective use of societal resources

K Ito, et al. J Clin Oncol 2012;30:1468-1475

Screening for osteoporosis – less is more ?

- Whether to screen postmenopausal women who are receiving AI
- How often to screen
- When to treat
- What type of treatment to initiate
  - Preferred route of bisphosphonate therapy (iv or oral) is unknown

Fulvestrant (Faslodex®)

- Work in a somewhat different way to block estrogen's effects
- Like SERMs, fulvestrant attaches to the estrogen receptor and functions as an estrogen antagonist
- However, unlike SERMs, fulvestrant has no estrogen agonist effects. It is a pure antiestrogen. In addition, when fulvestrant binds to the estrogen receptor, the receptor is targeted for destruction
- Called selective estrogen receptor down regulator (SERD)
- Has efficacy in tamoxifen-refractory disease and it has demonstrated an equivalent or superior activity than anastrozole in the metastatic cancers

Can hormonal therapy be used to prevent BC – Tamoxifen

- 由於在臨床上發現接受Tamoxifen治療的侵襲性或原位性乳癌患者，其對側乳房發生乳癌的機會較對照組有顯著降低，因此一般認為Tamoxifen可能可以降低高危險群病人的乳癌發生率
- 因此從1992年開始，美國國家外科輔助乳房及胃腸計劃(National Surgical Adjuvant Breast and Bowel Project，簡稱NSABP)組織進行一項乳癌預防臨床試驗(Breast Cancer Prevention Trial,簡稱BCPT; P-1 study)

Results of BCPT, P-1 study

Category of patient	Result: ↓ Risk by
Invasive BC	49% (p<0.00001)
Cumulative incidence	43.4 vs. 22 per 1000 women
Age ≤ 49	44%
50 – 59 yr	51%
≥ 60 yr	55%
Hx of LCIS	56%
Hx of atypical hyperplasia	86%
Predicted 5 yr risk	Any category
Noninvasive BC	50% (p <0.002)
ER positive tumour	69%

Study population N=13,388 (White 96.5%); 1. ≥ 60 yr, 2. 35-59 yr with a 5-yr predicted risk for BC of at least 1.66%, 3. Had Hx of LCIS. Tam x 5 yr vs. placebo

J Natl Cancer Inst. 1998 Sep 16;90(18):1371-88

Raloxifen (Evista 鈣穩錠)

- A 2nd generation SERM
- Initially developed for BC, later as alternative to hormonal replacement therapy for treatment of osteoporosis
- Similar activity to Tam in breast and bone, it is devoid of agonist activity in endometrium
- On September 13, 2007, the US FDA approved raloxifene (Evista®) for reduction in the risk of invasive BC in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive BC

Benefit of raloxifen

		Incidence of invasive BC		
Study	Patients	Raloxifen	Placebo	HR
MORE	5133	11 in 2557	38 in 2576	0.29
CORE	Subset of 4011 in MORE*	19 in 2716	20 in 1274	0.44
RUTH	10,101	40 in 5044	70 in 5057	0.56

***After a median of three additional years on treatment**

STAR trial

Patients = 19,747	Tamoxifen	Raloxifen
Intervention	20mg daily x 5 yr	60mg daily x 5 yr
Invasive BC (cases)	163	168
Non-invasive BC	57	80
Uterine cancer	36	23
Thromboembolic event		Occurred less often in the raloxifene group (RR, 0.70; 95% CI, 0.54-0.91)
Osteoporotc fracture	Similar	Similar
Cataracts	(RR, 0.79; 95% CI, 0.68-0.92)	

Raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer and has a lower risk of thromboembolic events and cataracts but a nonstatistically significant higher risk of noninvasive breast cancer. The risk of other cancers, fractures, ischemic heart disease, and stroke is similar for both drugs

JAMA. 2006;295(23):2727-2741

Updated results of STAR trial

	Risk ratio (raloxifen:tamoxifen)	95% confidence interval
Invasive BC	1.24	1.05-1.47
Noninvasive disease	1.22	0.95-1.59
Endometrial cancer	0.55	0.36-0.83; P = 0.003
Uterine hyperplasia	0.19	0.12-0.29
Thromboembolic events	0.75	0.60-0.93

Long-term raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive disease and grew closer over time to tamoxifen in preventing noninvasive disease, with far less toxicity (e.g., highly significantly less endometrial cancer). These results have important public health implications and clarify that both raloxifene and tamoxifen are good preventive choices for postmenopausal women with elevated risk for breast cancer

Cancer Prevention Research 2010; 3(6):696–706

BC prevention – Tamoxifen vs. Raloxifen

- Raloxifen potentially lost up to 35% of Tamoxifen effect on reduction of invasive BC
- Fewer noninvasive BC occurred in Tamoxifen group compared to raloxifen
- Raloxifen had lower incidence of deep vein thrombosis, pulmonary embolism, cataract and hysterectomy than Tamoxifen
- There is a trend of lower incidence of endometrial cancer
- An increased risk of death due to stroke was observed in a trial (on raloxifen) in postmenopausal women with documented coronary heart disease or at increased risk of major coronary events
- Other adverse reactions (>2% or more than placebo) include hot flashes, leg cramps, peripheral oedema, flu syndrome, arthralgia and sweating

Preventive effect of tamoxifen / raloxifen

- A meta-analysis of trials comparing Tam with placebo showed that Tam reduced the incidence of breast cancer by 38% with no effect on mortality
- On the basis of these collective data on Tam, the estimated no. needed to treat to prevent one BC after 5 yrs is about 95 and is reduced to 56 after 10 yrs
- Similar risk reduction occur with raloxifen

Lancet 2003;361:296-300
Cancer Prev Res (Phila) 2010;3:689-91
N Engl J Med 2006;355:125-37
J Natl Cancer Inst 2004;96:1751-61
JAMA 2006;295:2727-41

Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: A systematic review

- The RR for endometrial cancer in women <50 years given tamoxifen is 1.19 (95% CI, 0.53–2.65; $p = 0.6$) as compared to the placebo. The RR for deep vein thrombosis with tamoxifen is 2.30 (95% CI, 1.23–4.31; $p = 0.009$) in the active phase of treatment. The risk decreases to 1.00 (95% CI, 0.38–2.67; $p = 0.9$) in the follow-up phase. The RR for pulmonary embolism with tamoxifen is 1.16 (95% CI, 0.55–2.43; $p = 0.6$)
- Interpretation: The risk of endometrial cancer, deep vein thrombosis and pulmonary embolism is low in women <50 years who take tamoxifen for breast cancer prevention. The risk decreases from the active to follow-up phase of treatment. Education and counseling are the cornerstones of breast cancer chemoprevention

Cancer Treatment Reviews 2012;38:3180328

Exemestane for BC prevention in postmenopausal women

- Acceptance of tamoxifen or raloxifene for reducing risk of BC has been poor, in part because they are both associated with rare but serious toxic effects
- Both non-steroidal and steroidal AIs reduced contralateral primary BC more than did Tam; after 5 yr Tam, letrozole resulted in a further reduction of 46% as c/w placebo

BC prevention - exemestane

- Participants:
  - Women ≥ 35 yr if they were postmenopausal (> 50 yr with no menses > 12 m; ≤ 50 yr no menses within 12 m of randomization (spontaneous or secondary to hysterectomy) and FSH within post-menopausal range or with prior bilateral oophorectomy)
  - Had at least one of the following risk factors: ≥ 60 yrs, Gail risk score ≥ 1.66%, prior atypical ductal or lobular hyperplasia or LCIC on breast biopsy or DCIS treated with mastectomy

BC prevention - exemestane

Median fu 35m	Exemestane n=2285	Placebo n=2275
Invasive BC	11	32
Annual incidence	0.19%*	0.55%
Ductal carcinoma	10	27
Lobular carcinoma	2	5
ER+	7	27
ER-	4	5
DCIS	9	14
Invasive + DCIS	20	44 (? 46)
Annual incidence	0.35%#	0.77%

HR* 0.35, 95% CI 0.18 – 0.70, P= 0.002; HR# 0.47, 95% CI 0.27 – 0.79, P= 0.004

The number needed to treat to prevent one case of invasive BC with exemestane therapy was 94 in 3 years and 26 in 5 years, but few women completed 5 years of therapy

No significant differences between the two groups in terms of skeletal fractures, cardiovascular events, other cancers, or treatment-related deaths. Minimal QoL differences were observed

THANK YOU