乳癌手術後之荷爾蒙治療及趨勢

Hormonal Therapy After Breast Cancer Surgery And Its Development

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荷爾蒙輔助治療適合那些乳癌病人服用？(Who)

賀爾蒙療法

- 中斷供應雌激素給癌細胞，從而阻止癌細胞生長口服藥
- 適用於：雌激素受體 陽性
- 目的：清除微量轉移，減低復發率，提高存活率
- 療程最少五年

Breast Cancer Biologic Markers – Immunohistochemical Studies

Estrogen receptor (ER) score:

	Invasive component	In-situ component
Proportion score (PS)	5	5
Intensity score (IS)	2	2
Allred score (PS + IS)	7	7
Interpretation (Allred score)	☐ Negative (0, 2) ☑ Positive (3-8)	☐ Negative (0, 2) ☑ Positive (3-8)
Corresponding H-score (0-300)	180	180

Progesterone receptor (PR) score:

	Invasive component	In-situ component
Proportion score (PS)	4	4
Intensity score (IS)	3	3
Allred score (PS + IS)	7	7
Interpretation (Allred score)	☐ Negative (0, 2) ☑ Positive (3-8)	☐ Negative (0, 2) ☑ Positive (3-8)
Corresponding H-score (0-300)	85	85

For ER and PR score: Proportion score: 0 = None; 1 = >0-1%; 2 = >1-10%; 3 = >10-33.3%; 4 = >33.3-66.7%; 5 = >66.7%
Intensity score (average staining intensity of all positive tumour cells):0 = None; 1 = Weak; 2 = Intermediate; 3 = Strong

Ki-67 index:

	Invasive component	In-situ component
Ki-67 index	40%	25%
Interpretation	☐ Low proliferative index ☑ High proliferative index (>12-16%)	☐ Low proliferative index ☑ High proliferative index (>12-16%)

HER2/c-erbB2 overexpression:

	Invasive component	In-situ component
Score	2	2
Interpretation	Score 0 = Negative (No staining, or membrane staining in < 10% tumor cells) Score 1 = Negative (Faint membrane staining in > 10% tumor cells; cells are only stained in part of their membrane) Score 2 = Weakly positive (Weak to moderate staining of entire membrane in >10% tumor cells) Score 3 = Strongly positive (Moderate to strong staining of entire membrane in >30% tumor cells)	

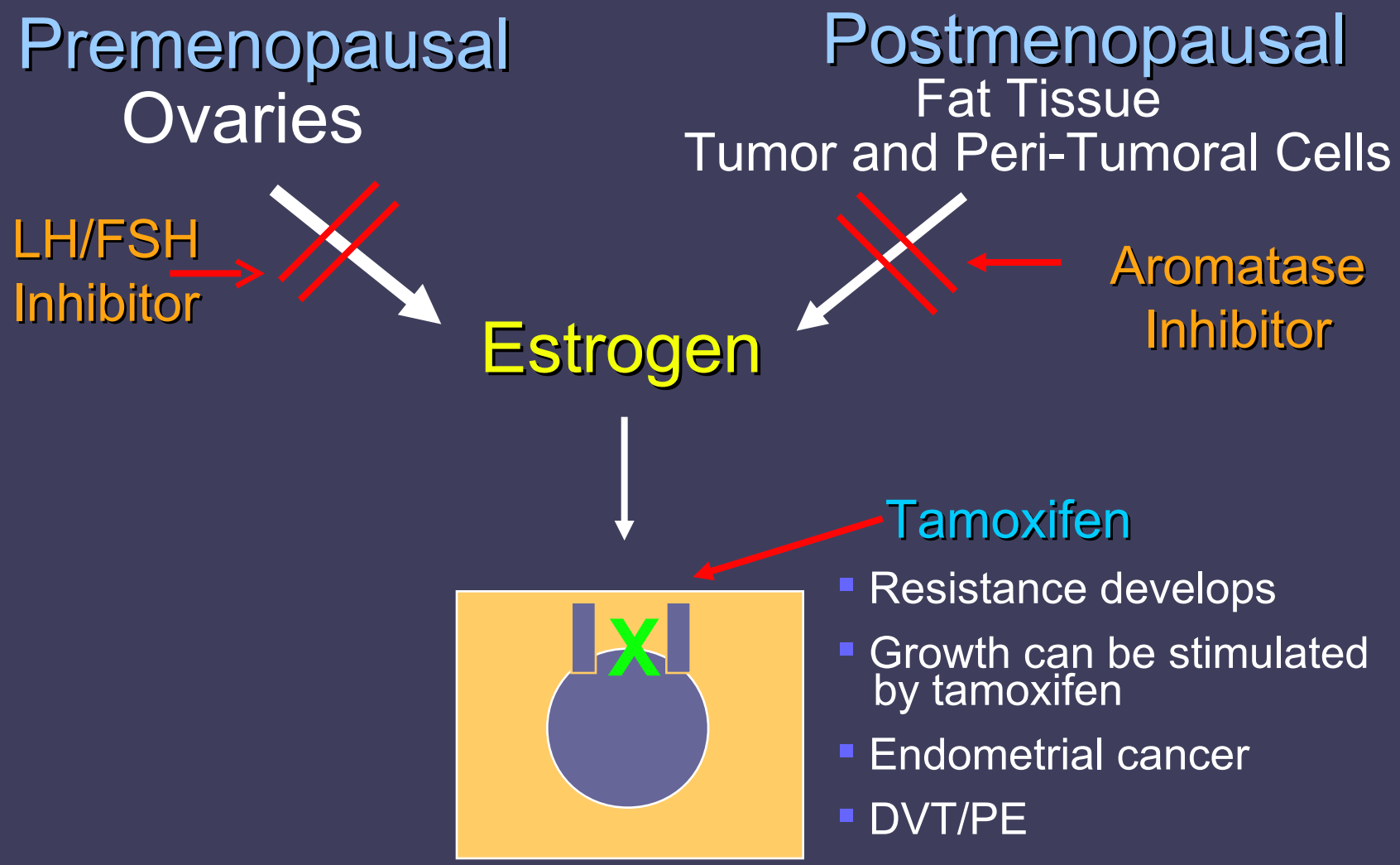
Summary:

	Result	Score
Estrogen receptor	Positive	Allred: 7/8 H-Score: 180/300
Progesterone receptor	Positive	Allred: 7/8 H-Score: 85/300
Ki-67 proliferation marker status	High proliferative index	40%
HER2 (c-erbB-2) oncoprotein overexpression	Weakly positive	2

Note: The above summary pertains to the invasive component.
Because of the finding of weakly positive (score 2) HER2 (c-erbB-2) oncoprotein overexpression, in situ hybridization study will be performed to determine if there is HER2 (c-erbB-2) gene amplification. A report will follow.

(IHC test performed by Pathology Department, QEH, ref. No.: C424-10)

Antagonizing Estrogen



Anti-estrogen Therapy
荷爾蒙治療

First Targeted Therapy!

最早的標靶治療！

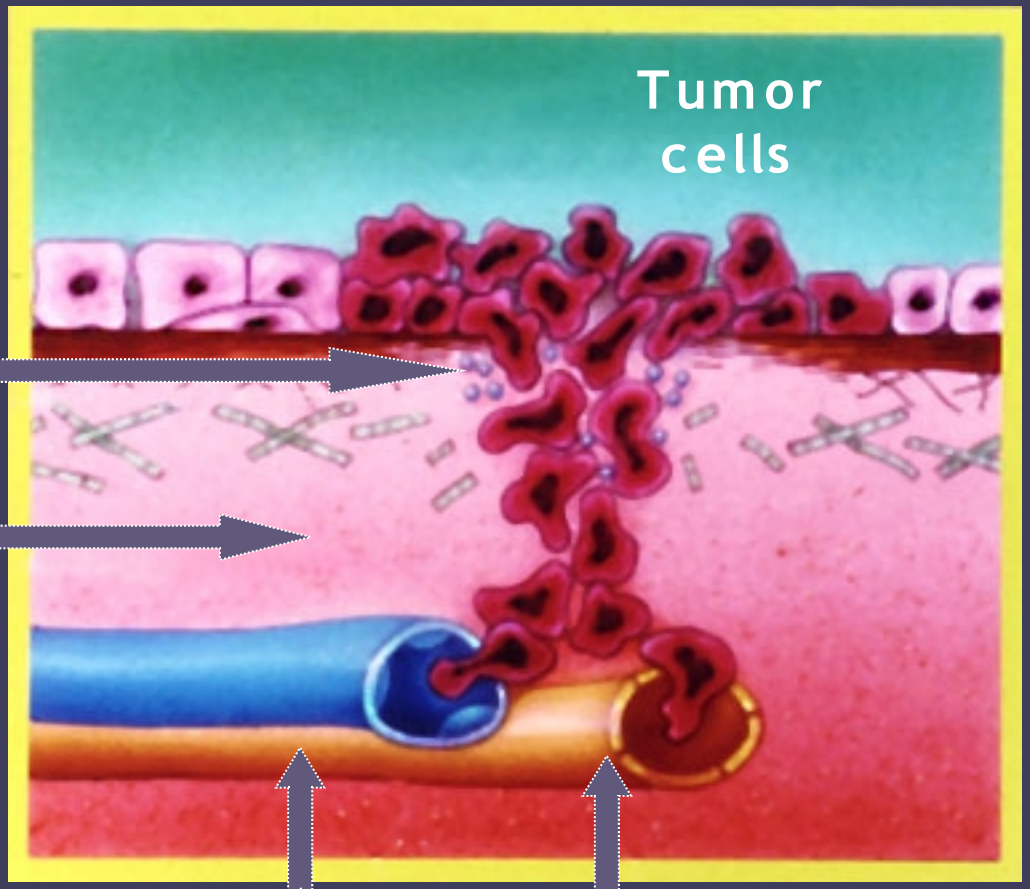
Development of Endocrine Therapy

1896	Oophorectomy
1922	Ovarian irradiation
1939	Androgens
1944	Synthetic estrogens
1951	Progestins
1952	Pituitary irradiation
1953	Adrenalectomy, Hypophysectomy
1971	Antiestrogens
1973	Aromatase inhibitors/inactivators
1982	LHRH-agonists
1987	Antiprogestins
1993	“Pure” antiestrogens

Reference: Howell A, et al. Reviews on Endocrine-related Cancer 1993; 43: 5-21.

為何乳癌手術後需要荷爾蒙輔助治療 (Why)

DIAGRAM OF THE METASTATIC PROCESS BY THE ACTION OF PROTEASES



asion of the blood and lymph systems occur simultaneo

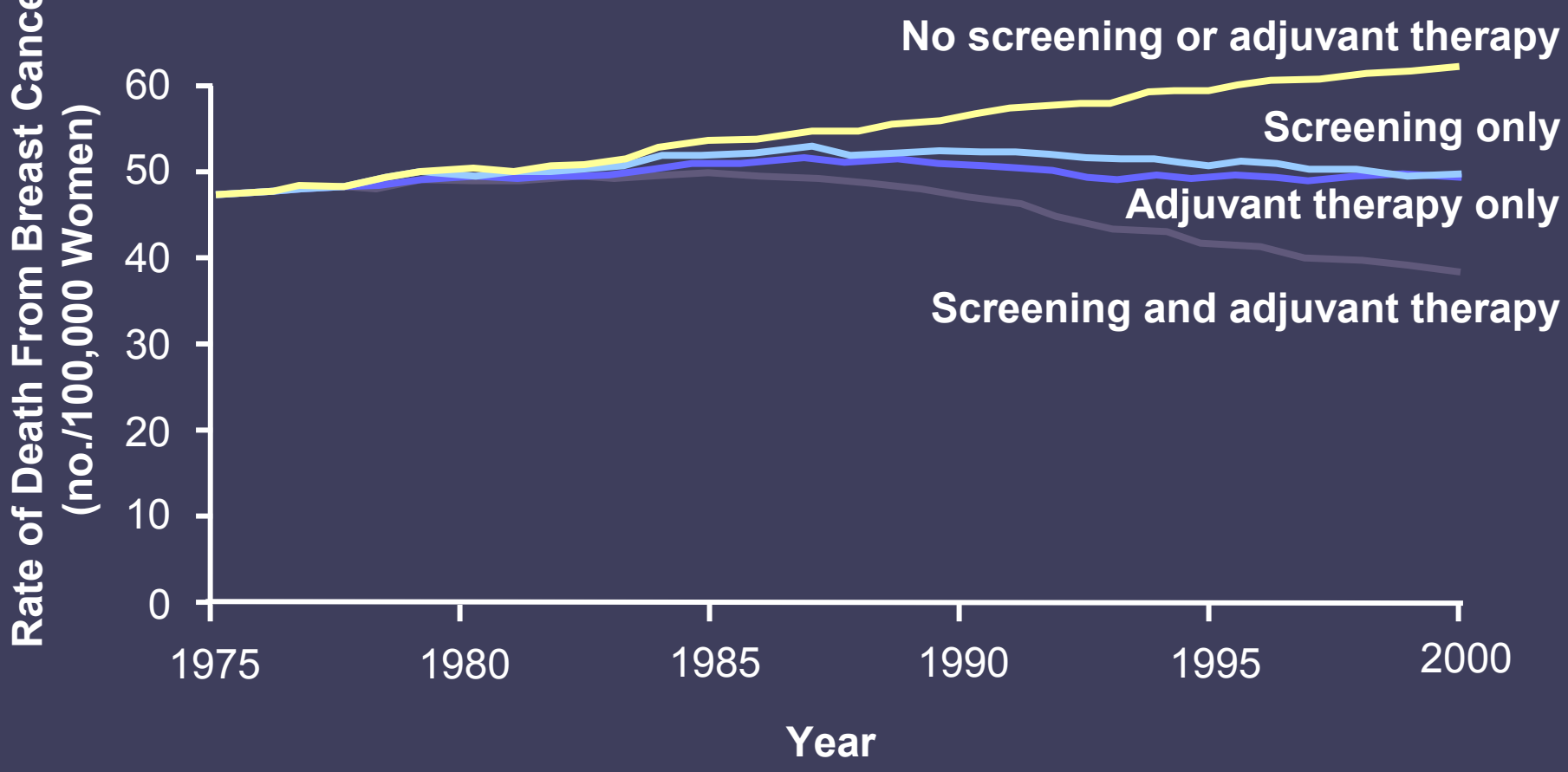
為何切除乳癌腫瘤後仍有復發機會？

- 手術時可能癌細胞未被徹底消滅
- 癌細胞已經轉移到淋巴結或內臟
- 輔助性治療未能徹底消滅癌細胞
- 會增加乳癌復發率的潛在因素：
  - 年齡在 35 歲以下的女性
  - 癌症腫瘤較大
  - 有淋巴結轉移的病者

因此 ， 乳癌手術後 ， 病人仍需採取相應的輔助治療 ，以減低乳癌復發風險。

Estimated Mortality Trends

Value of Screening Mammography and Adjuvant Treatment

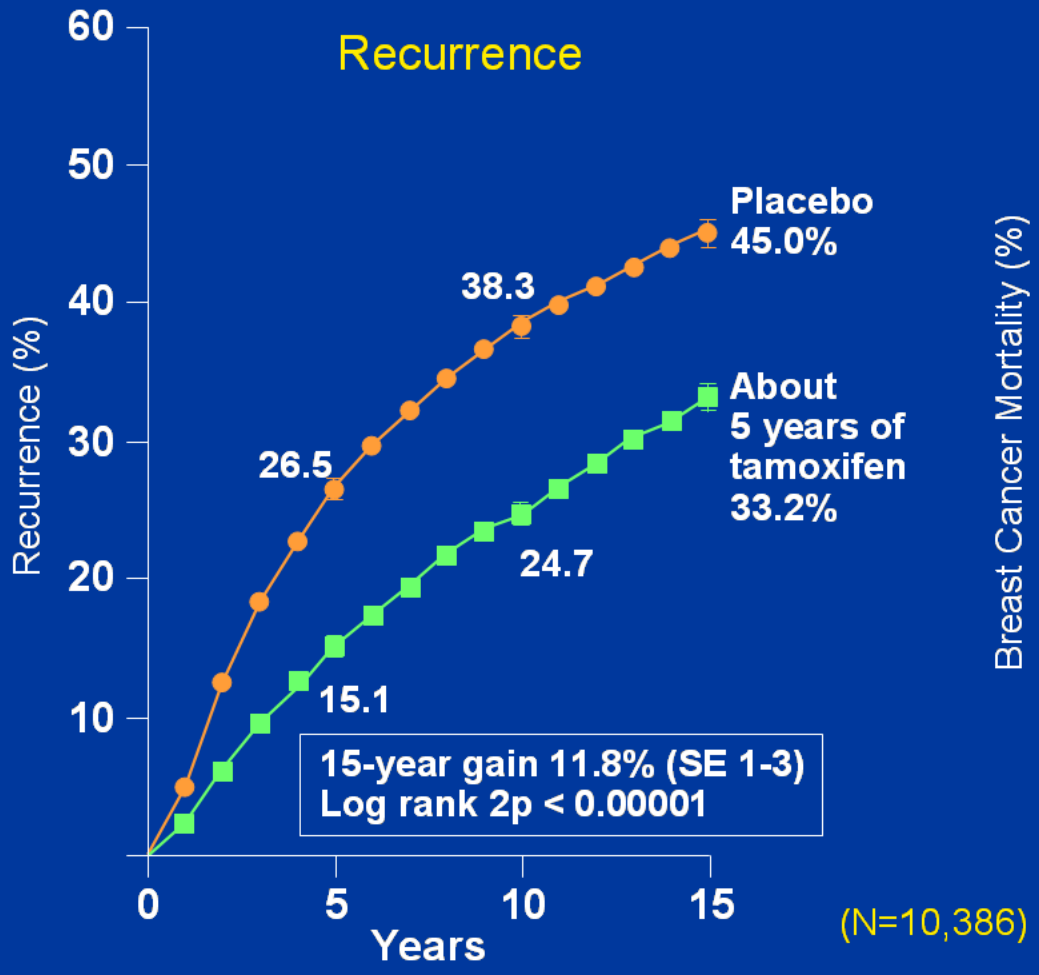


Berry et al. *N Engl J Med*. 2005;353:1784-1792 (C).

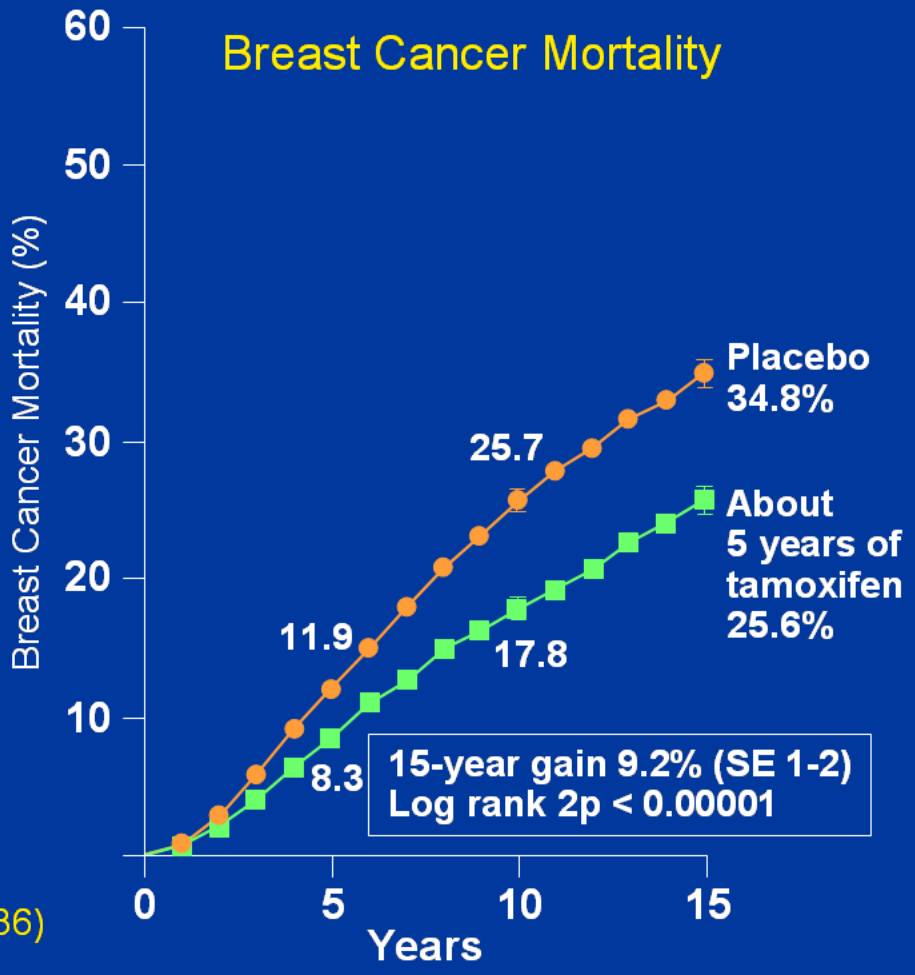
Strategies to Improve Outcome

- Screening
- Surgery, Radiation
- Adjuvant chemotherapy
- Adjuvant targeted
- **Adjuvant endocrine**

EBCTCG Meta-Analysis: Adjuvant Tamoxifen Improves 15-Year Disease-Free and Overall Survival in Women With ER-Positive Early Breast Cancer

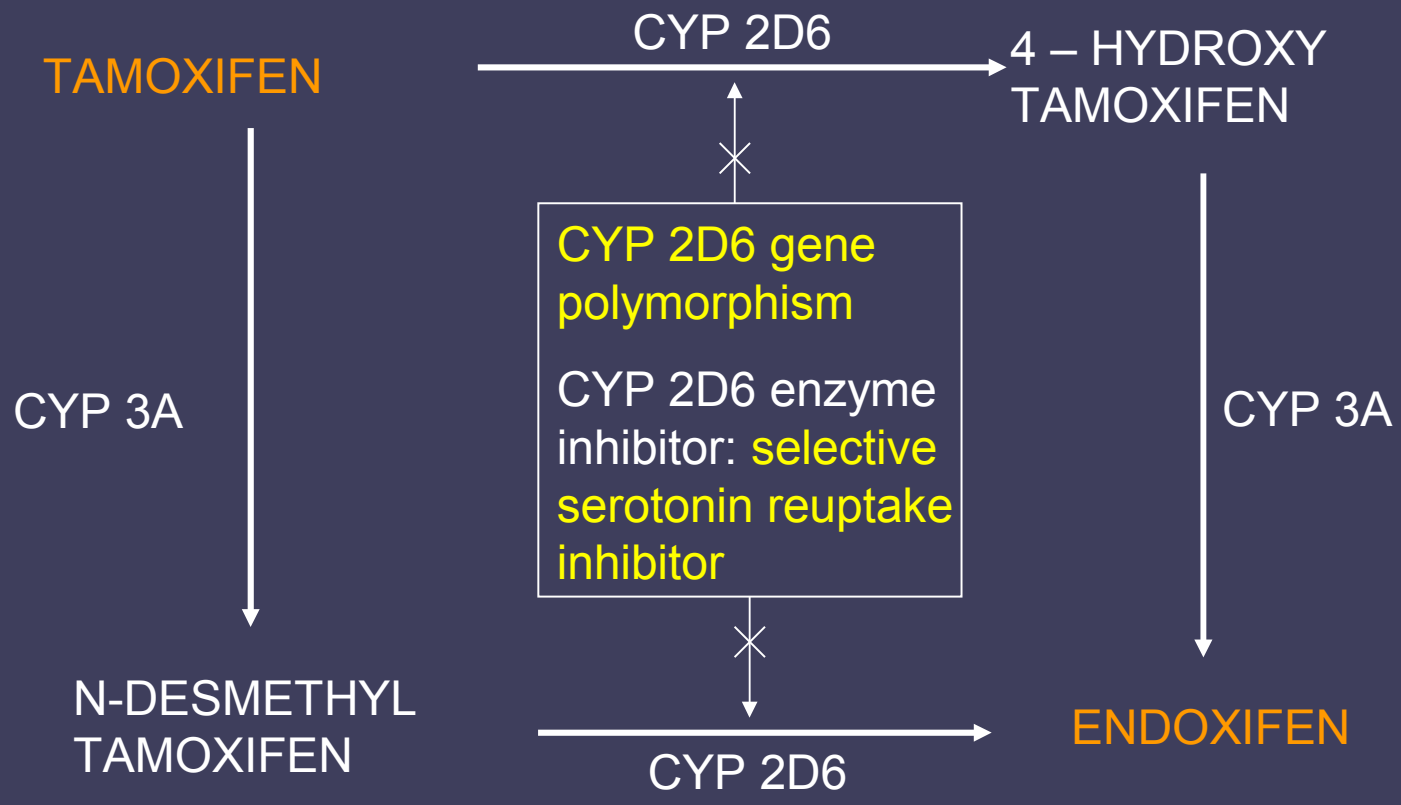


(N=10,386)



Adapted from EBCTCG. *Lancet.* 2005;365(9472):1687-1717.

CYP 2D6 Genotype, Antidepressant Use and Tamoxifen Metabolism During Adjuvant Breast Cancer Treatment

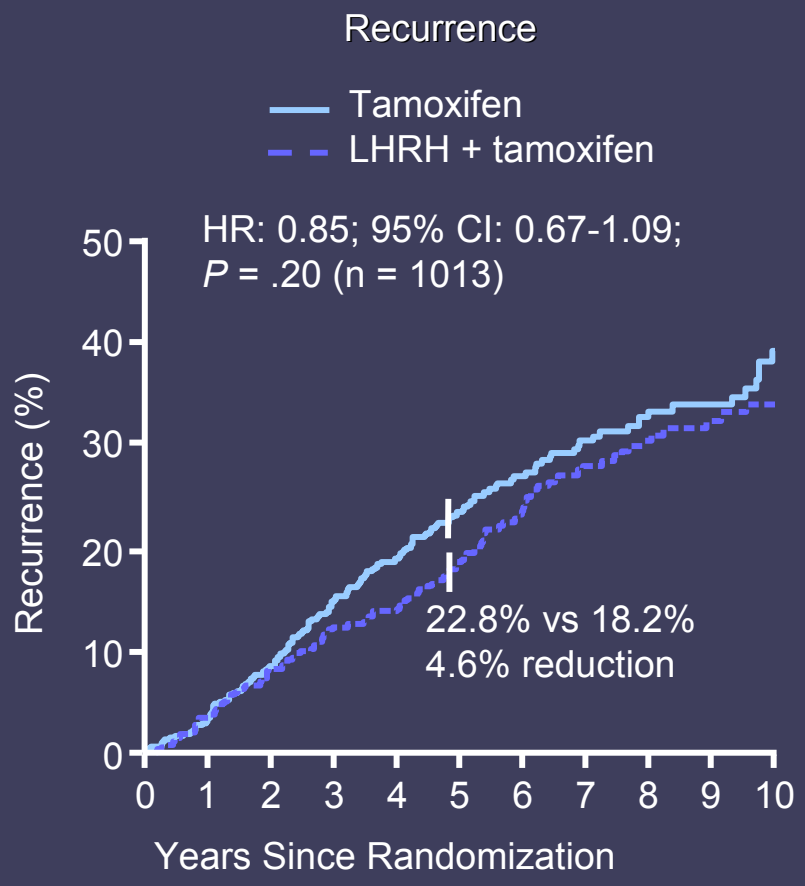


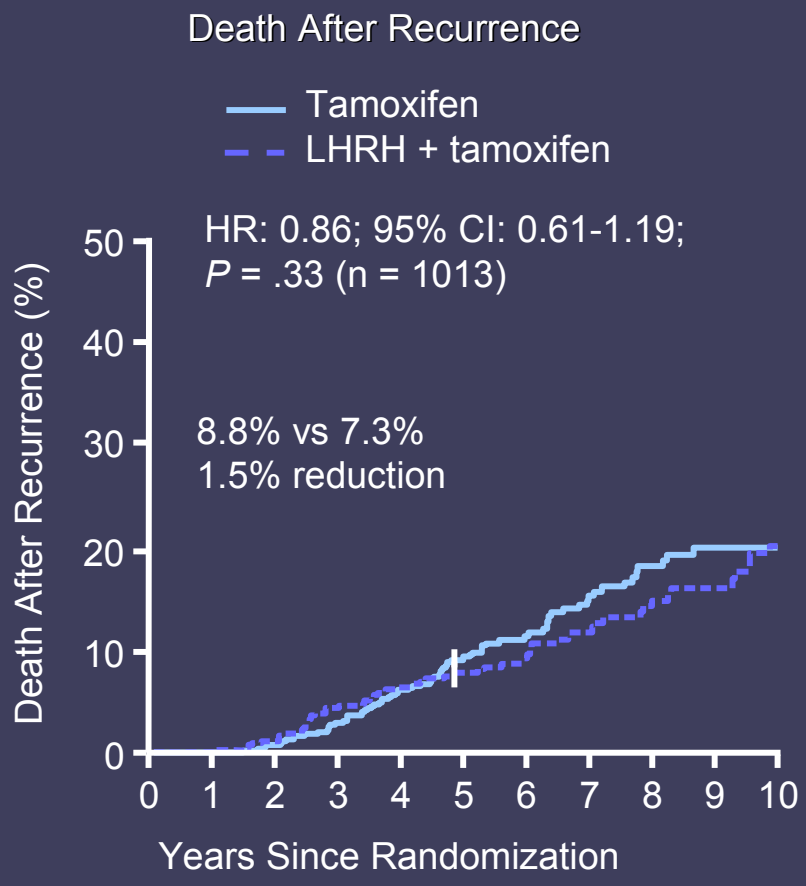
JNCI, Vol. 97, No. 1, 30-39; 2005

Can We Improve on TAM?

- Total oestrogen blockade
- Using AI?
- TAM longer than 5 years?
- Adding AI after 5 years of TAM?

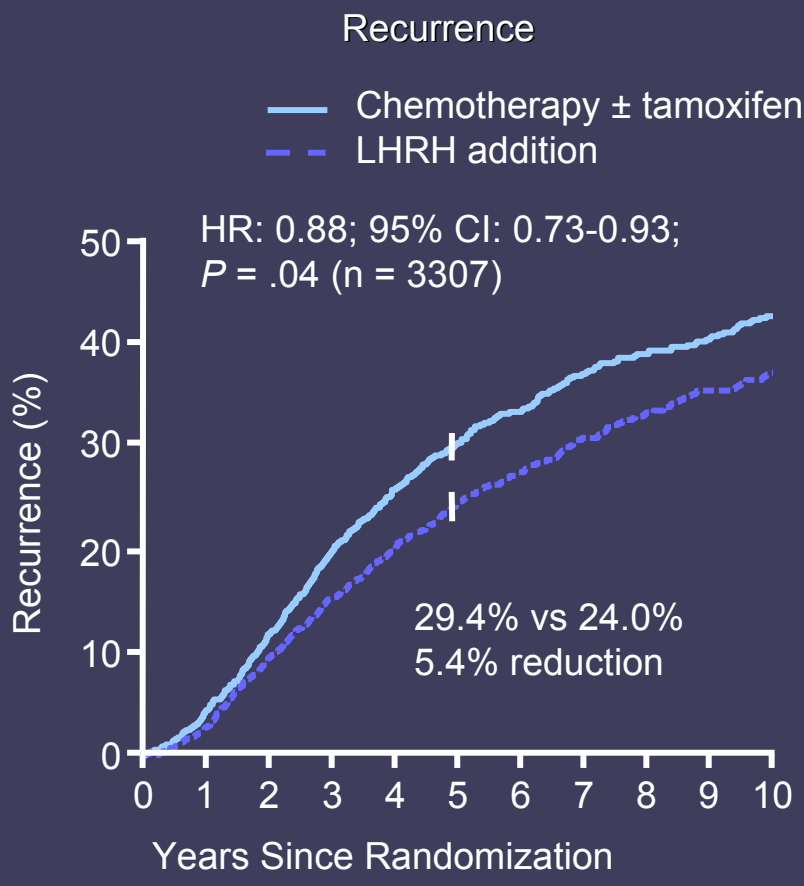
Small, Nonsignificant Clinical Benefit of Adding LHRH Agonist to Tamoxifen

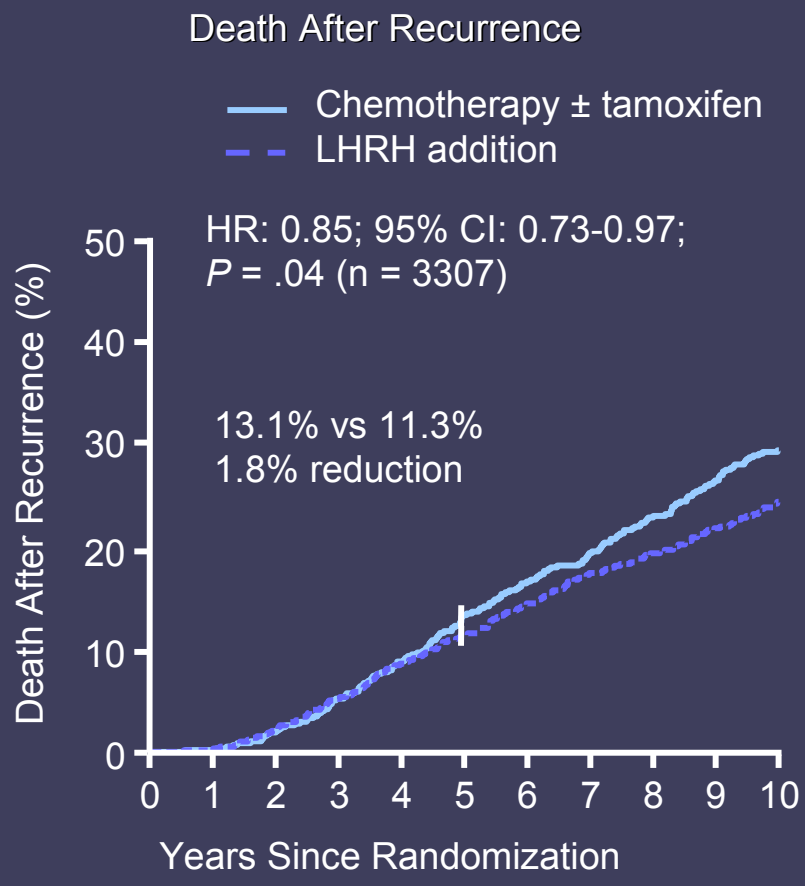




Cuzick J, et al. SABCS 2006. Abstract 15.

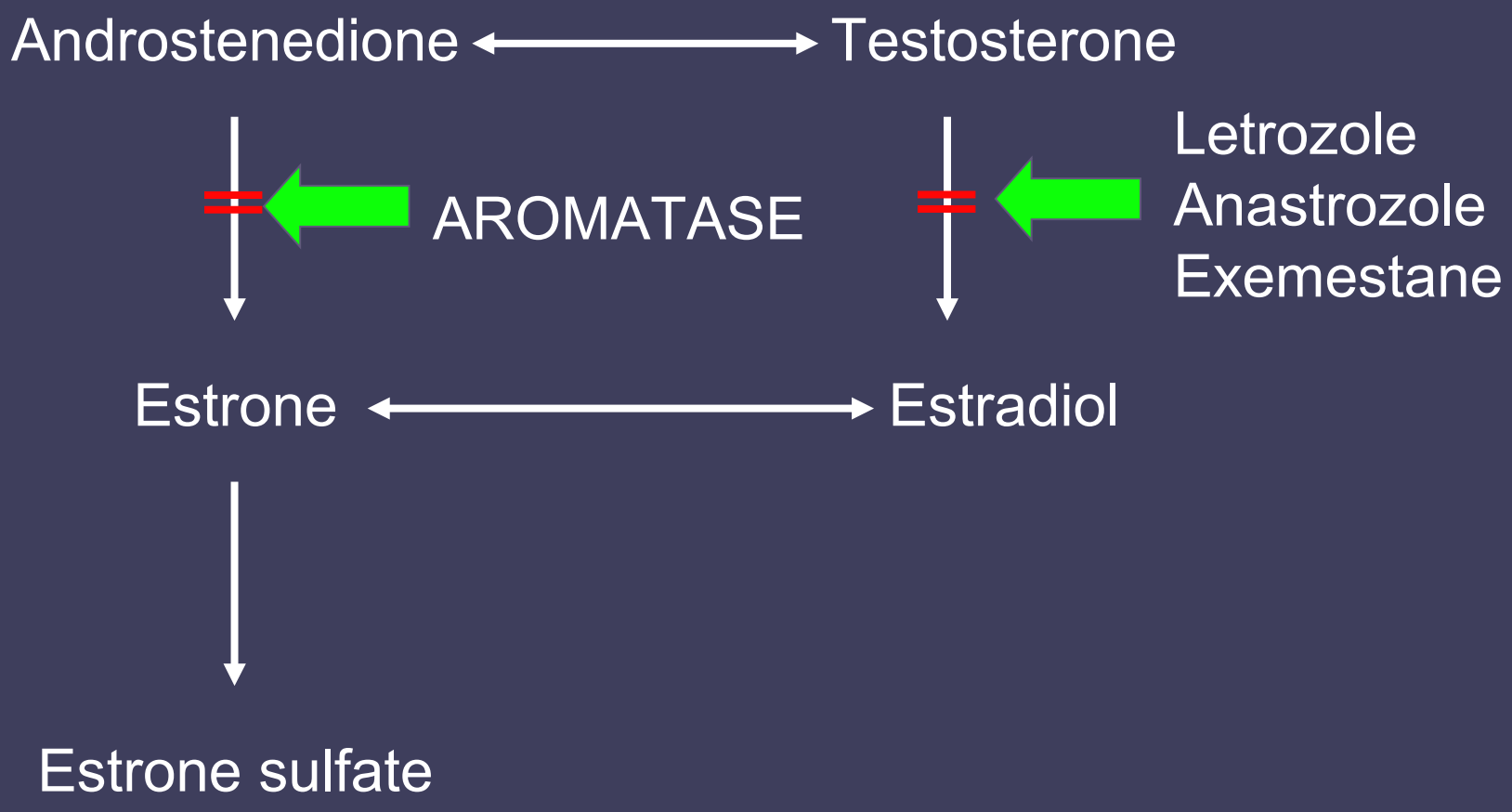
Significant Clinical Benefit of Adding LHRH Agonist to Chemotherapy





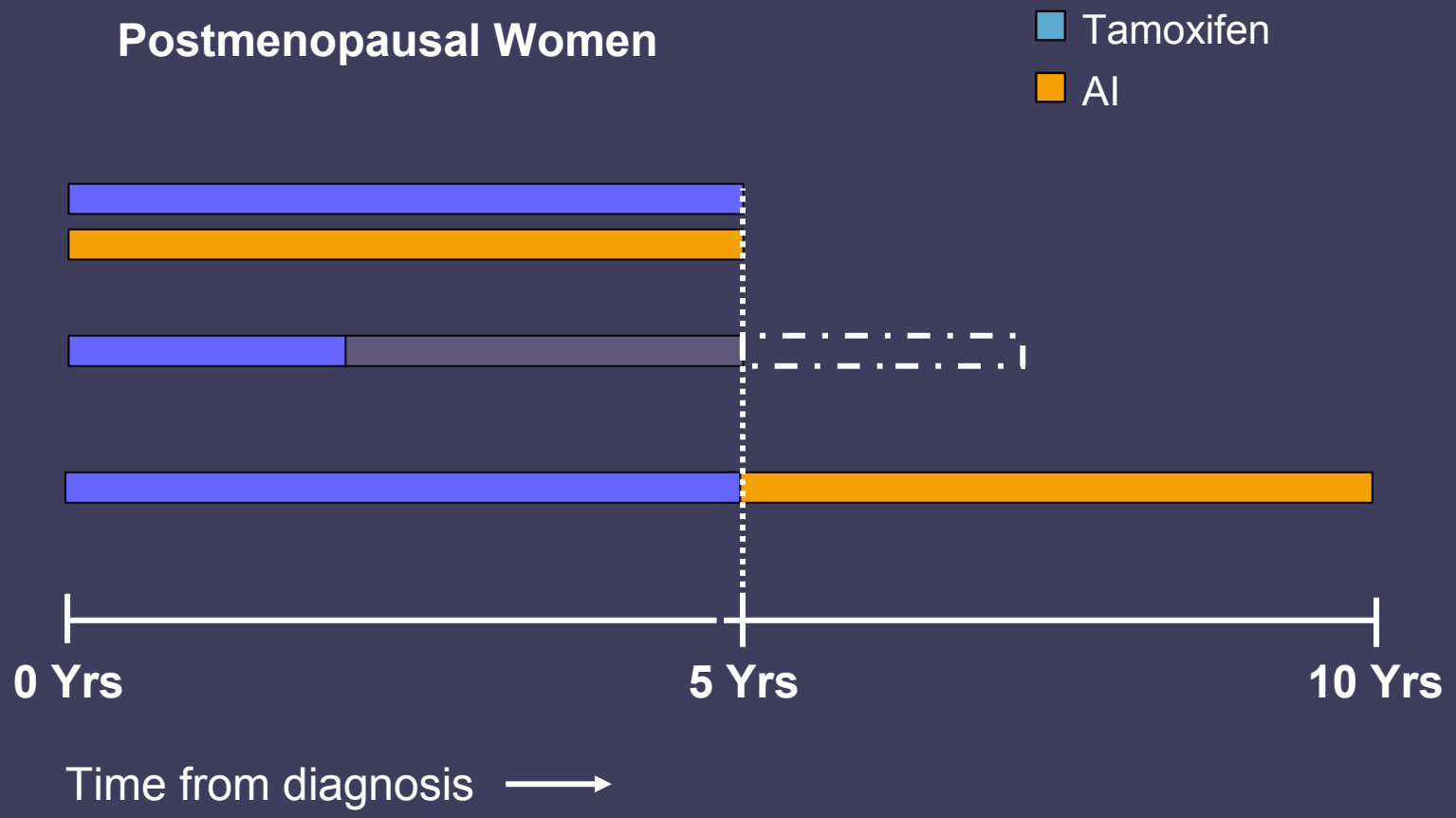
Cuzick J, et al. SABCS 2006. Abstract 15.

Inhibition of Aromatase

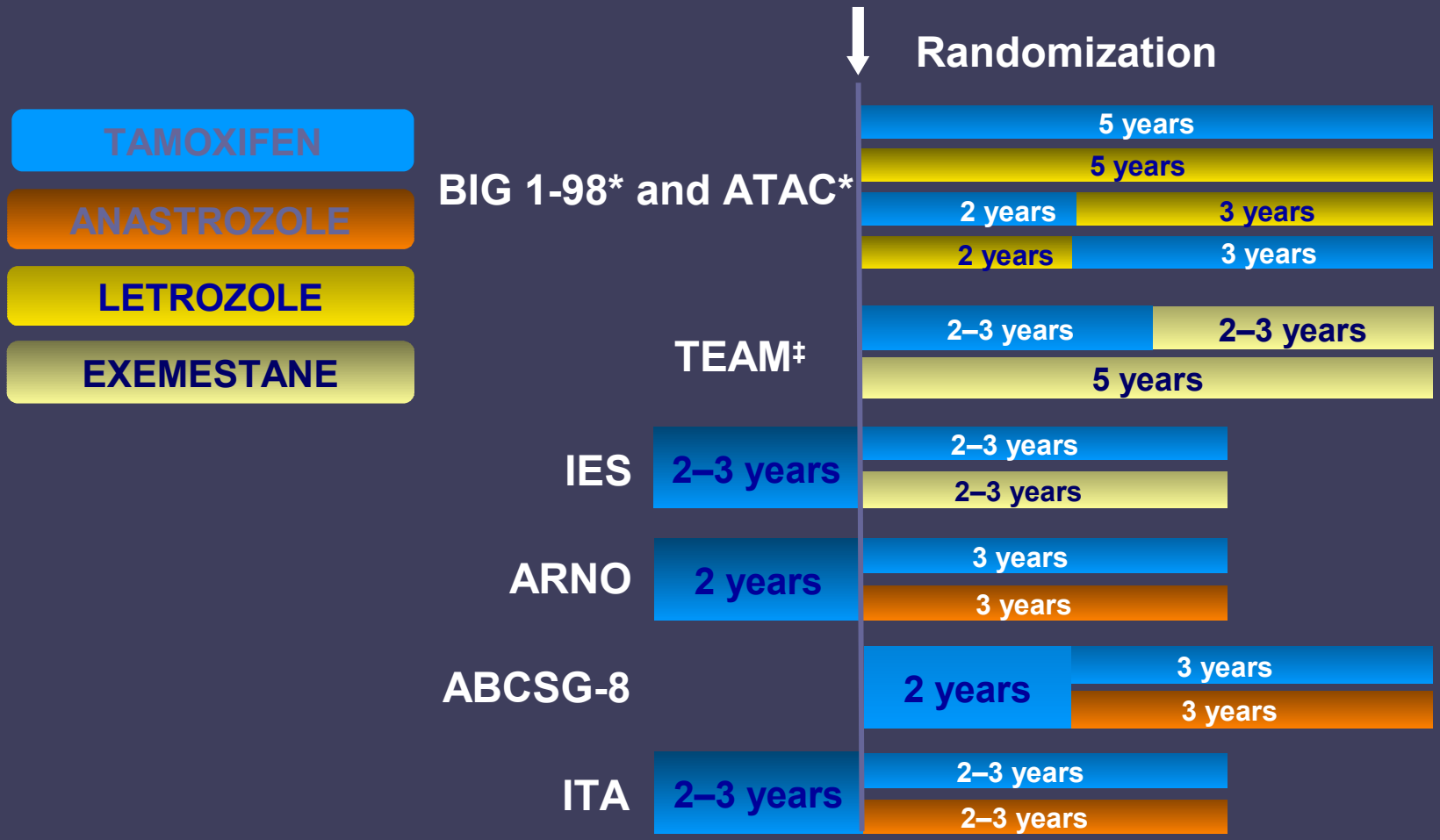


Efficacy Overview: Adjuvant Trials Using AI

Current Adjuvant Endocrine Therapies

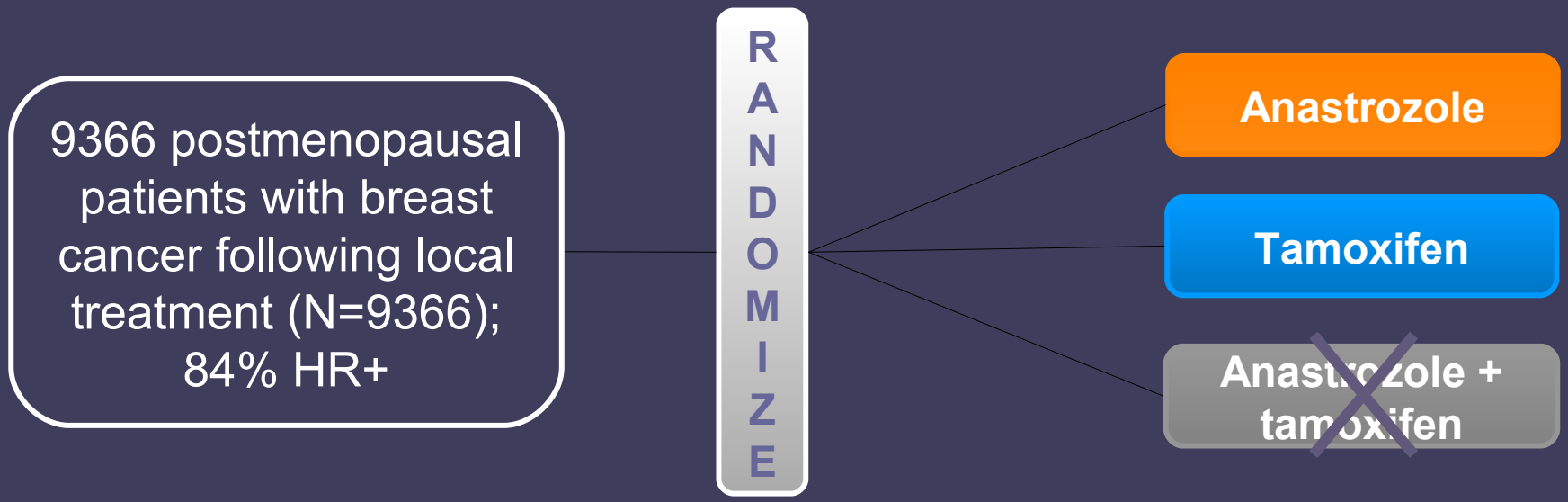


Treatment Strategies Studied in Adjuvant AI Trials



*Registration trials; †Combination arm discontinued at first analysis;
**ABCSG: randomization immediately after surgery; ARNO: randomization up to 2 years after surgery;
‡TEAM protocol altered to affect switch to Exem after 2–3 years' TAM.

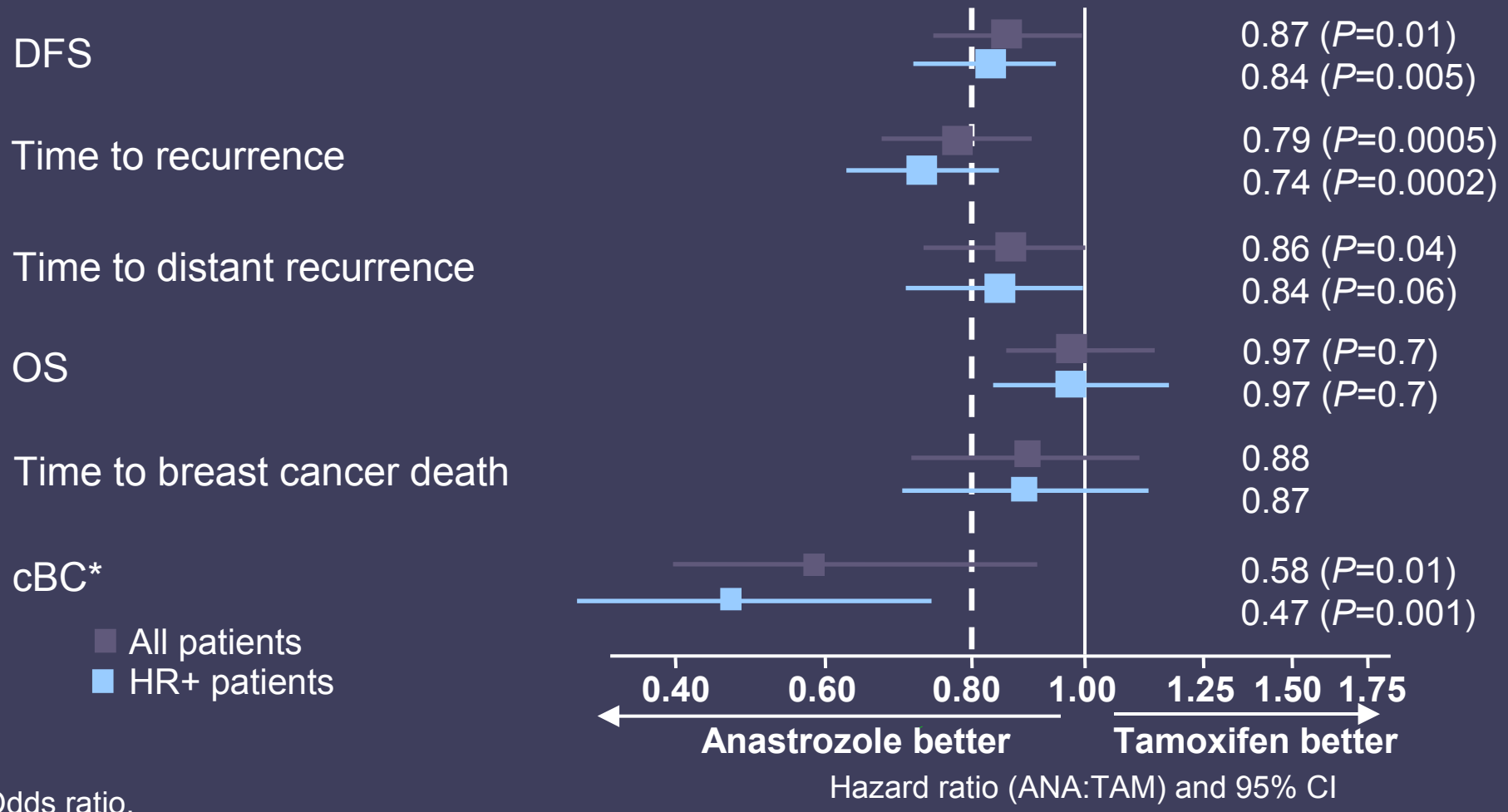
ATAC: Arimidex®, Tamoxifen, Alone or in Combination



- **Primary end point**: DFS, defined as time to earliest occurrence of local or distant recurrence, new primary contralateral breast cancer, or death from any cause

Howell et al. *Lancet*. 2005;365:60.
Update of Howell et al. *Breast Cancer Res Treat*. 2004;88(suppl 1):S7. Abstract 1.

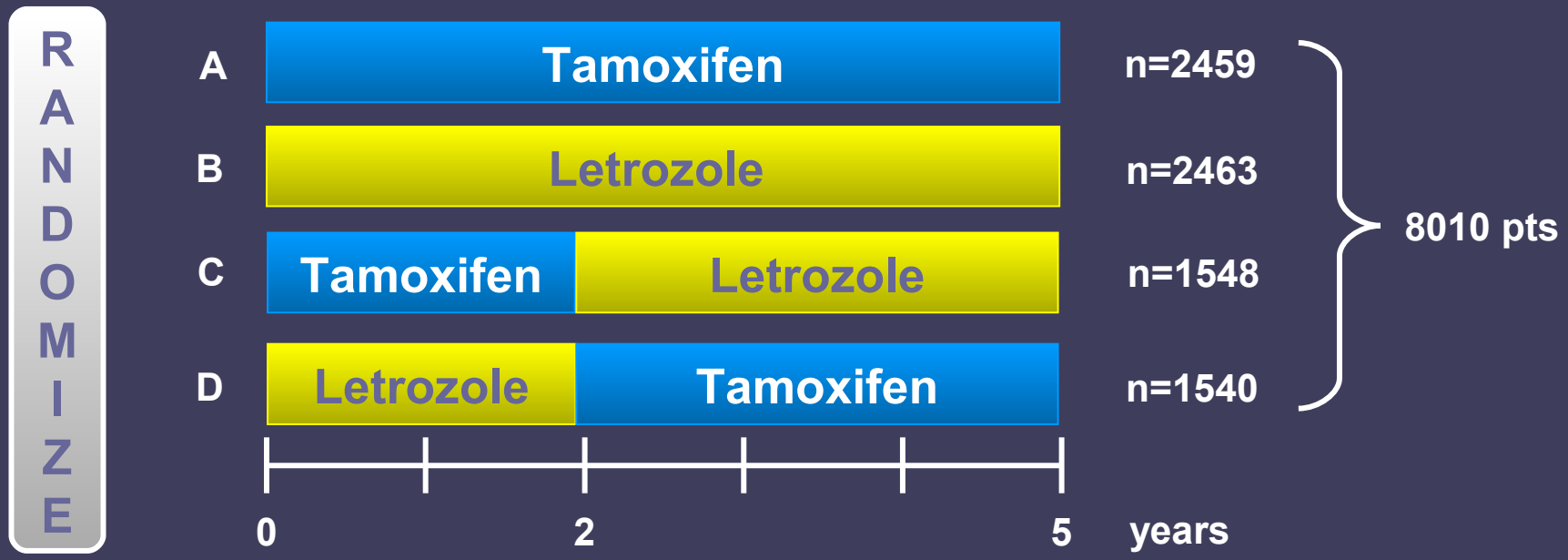
ATAC: Efficacy End Points at 68 Months' Median Follow-up



*Odds ratio.
cBC = contralateral breast cancer; CI = confidence interval.

Howell et al. *Lancet.* 2005;365:60.

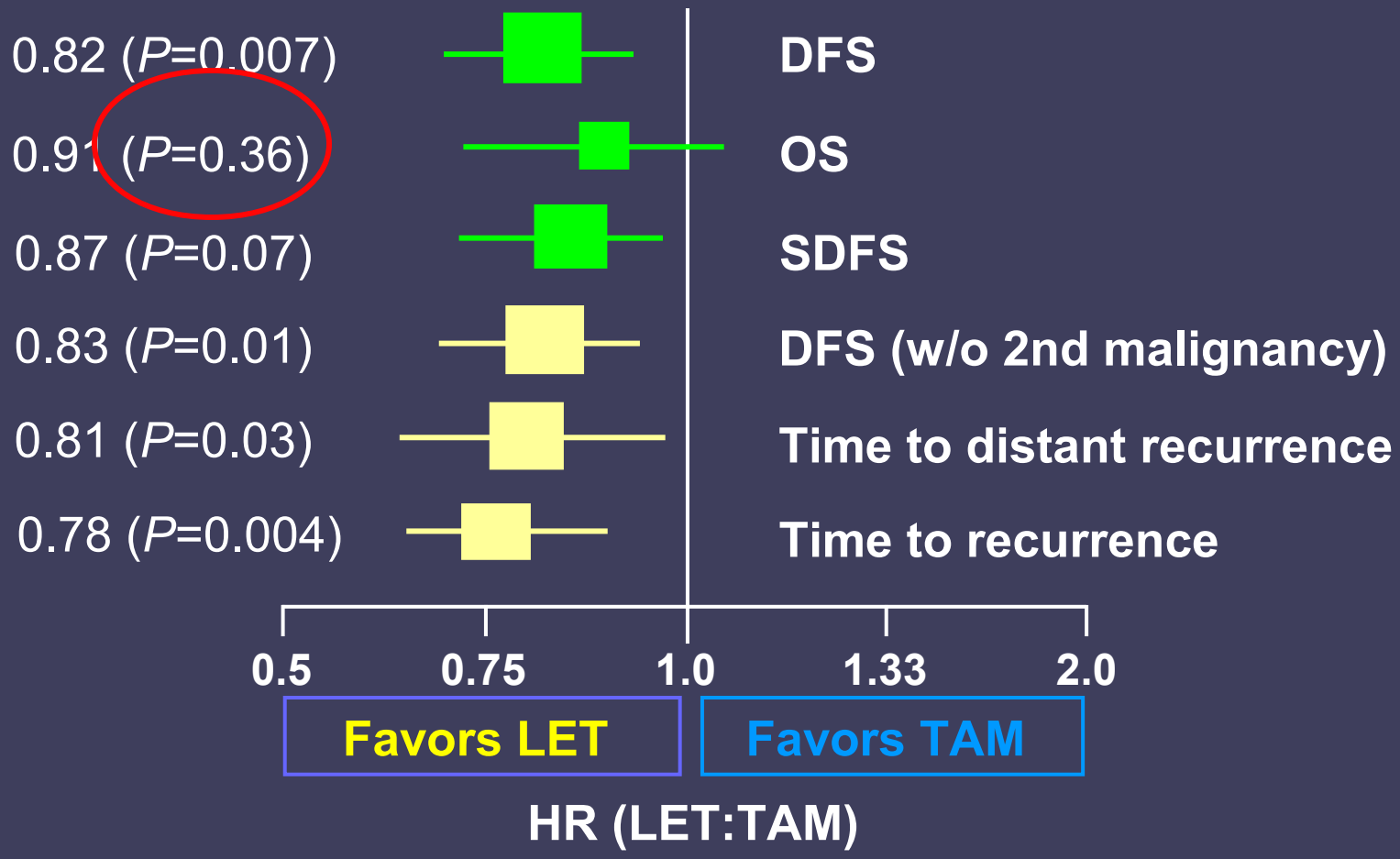
BIG 1-98: Trial Design



- Primary core analysis (both circles) compares tamoxifen vs letrozole monotherapy, including arms C and D prior to the switch at 2 years
  - Median follow-up 25.8 months (n=4007 tamoxifen; n=4003 letrozole)
- Monotherapy-only analysis (top circle)
  - Median follow-up 51 months (n=2459 in A; n=2463 in B)

Coates et al. *J Clin Oncol*. 2007;25:486.
Thürlimann et al. *N Engl J Med*. 2005;353:2747.

BIG 1-98: 51-Month Monotherapy-Only Efficacy End Points

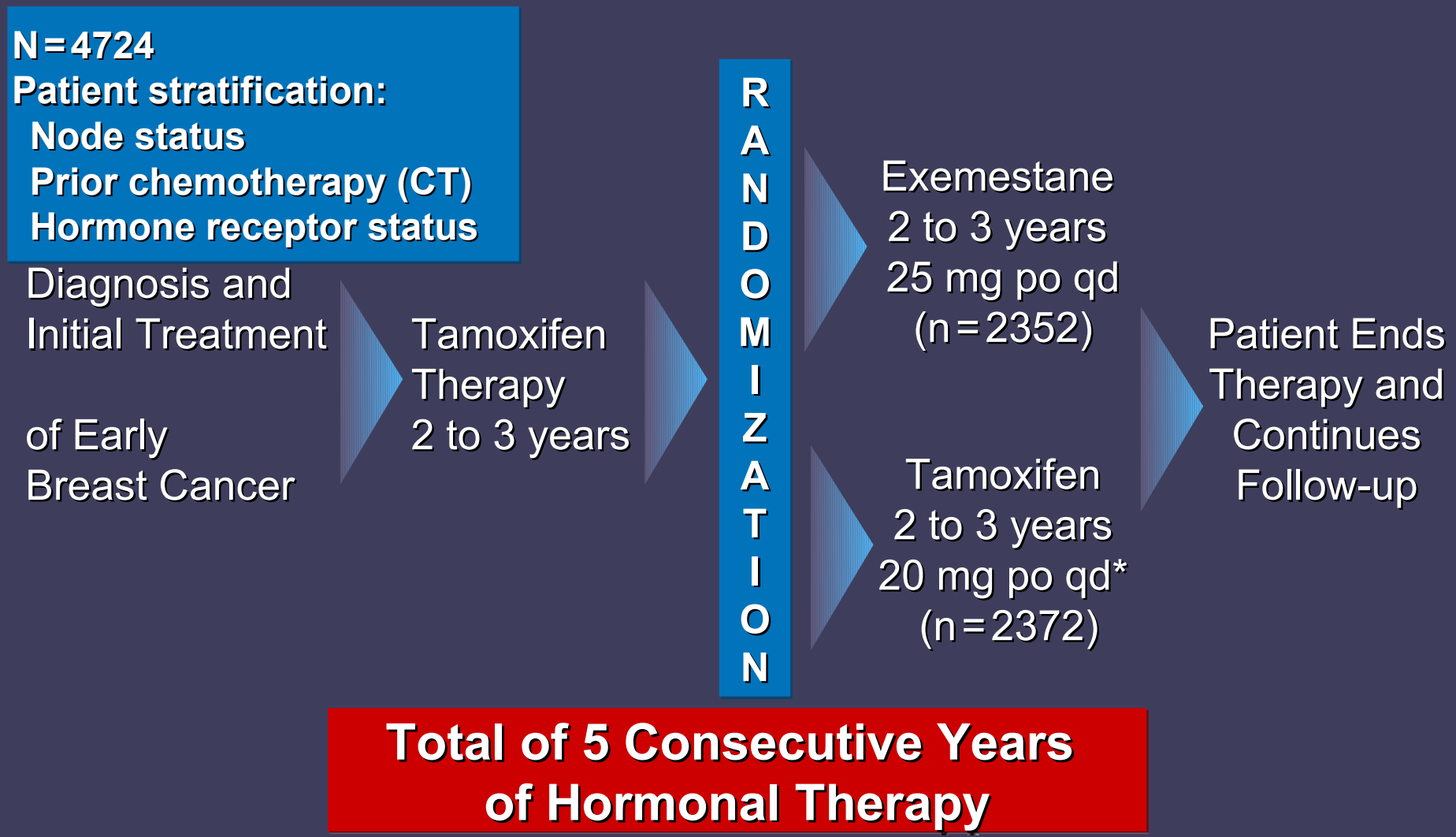


SDFS = systemic DFS.

Coates et al. *J Clin Oncol.* 2007;25:486.

IES Trial Design

Multinational, Double-Blinded, Randomized Trial



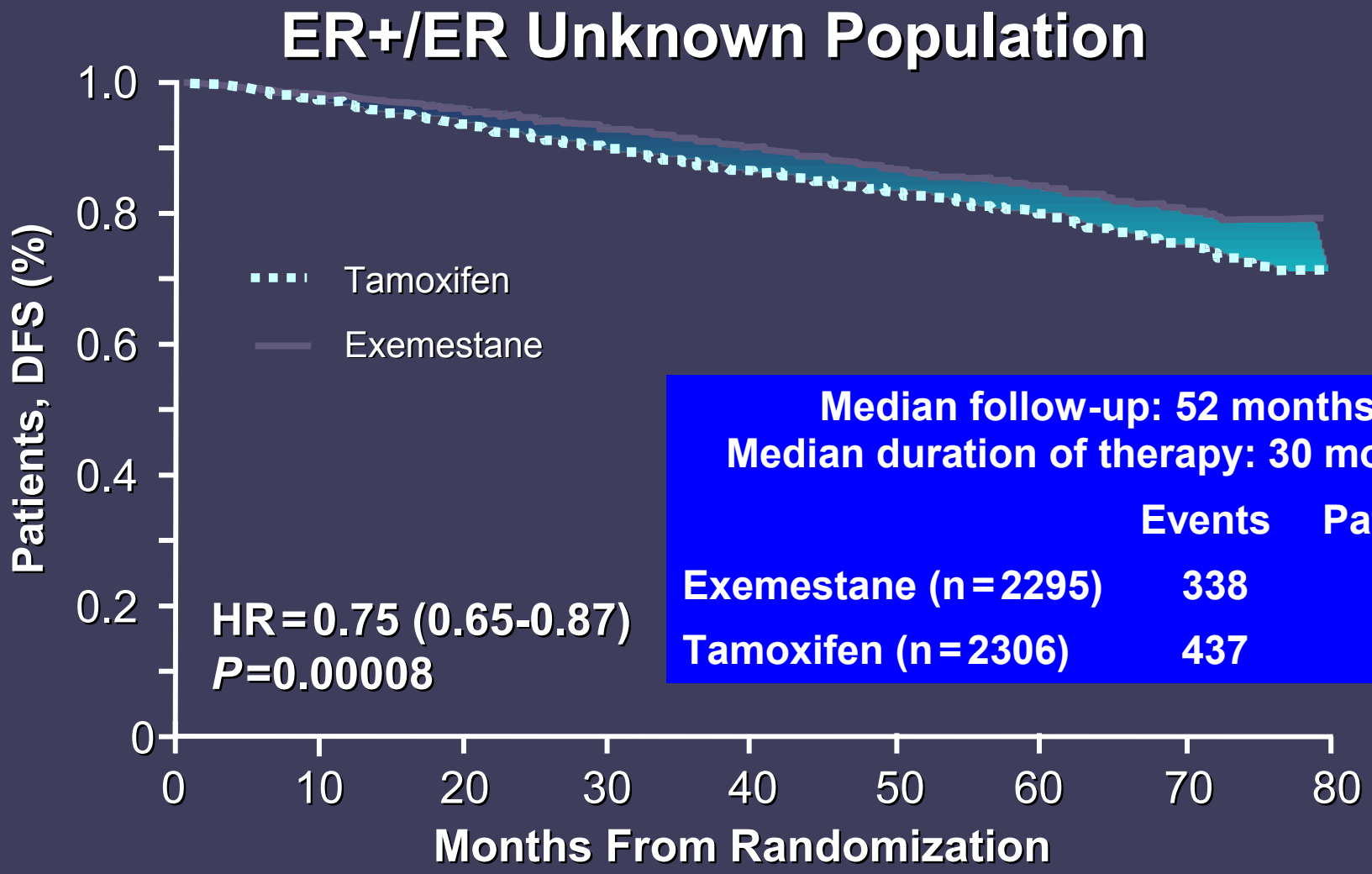
*Approximately 3% of patient population received tamoxifen 30 mg po qd.
Median follow-up 34.5 months. *Please see full prescribing information.*

Efficacy Results at 52.4 Months: ER+/ER Unknown Population

ER+/ER Unknown Population	HR*	95% CI	*P* Value
DFS	0.75	0.65-0.87	0.00008
CLBC	0.54	0.31-0.94	0.027
Distant RFS	0.82	0.69-0.97	0.02
Overall survival	0.83	0.69-.99	0.04

*When interpreting the HR information, it is important to note that on average patients had stopped taking either tamoxifen or Exemestane therapy for 25 months.

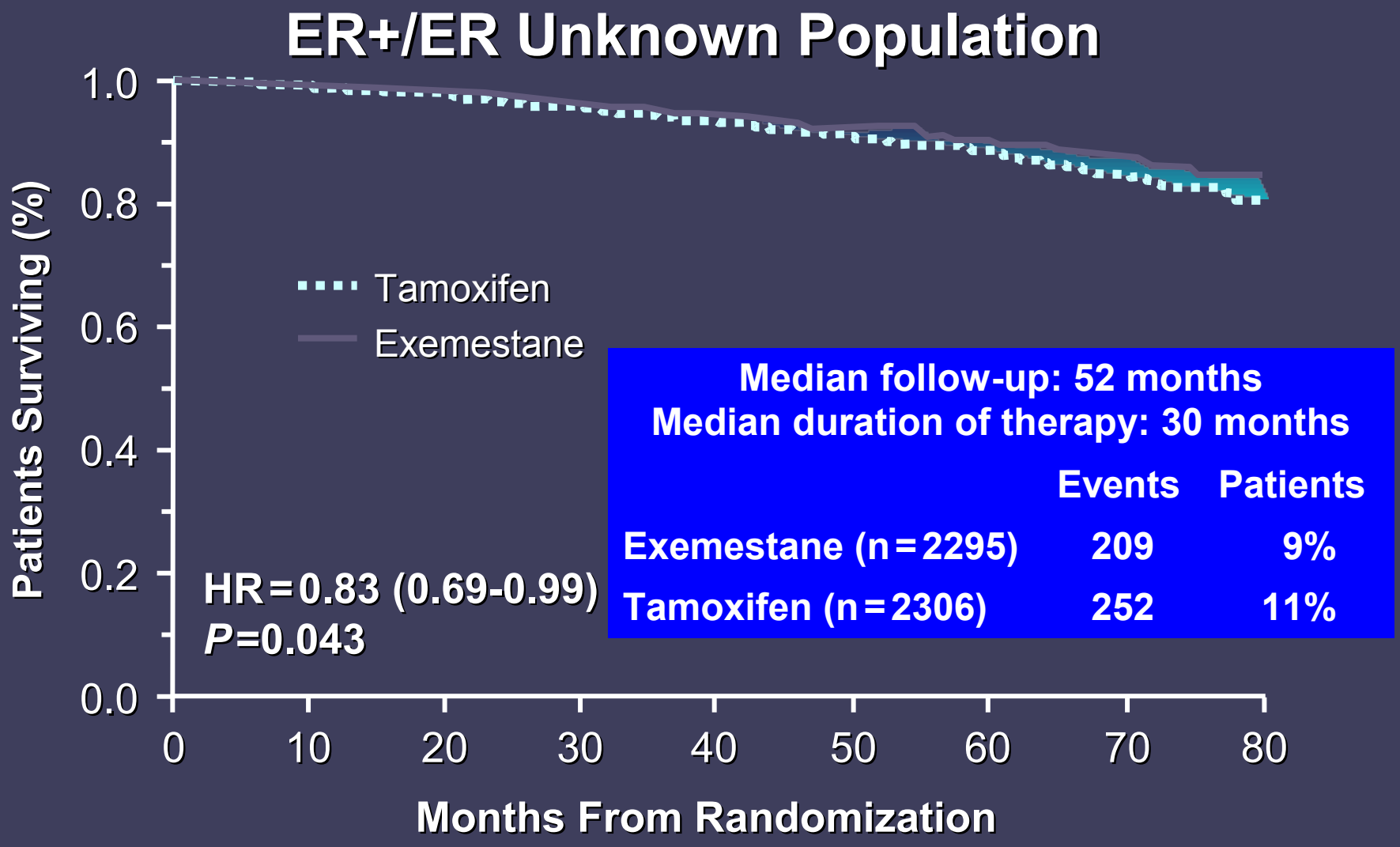
Disease-Free Survival: 52.4 Months



Median follow-up: 52 months
Median duration of therapy: 30 months

	Events	Patients
Exemestane (n = 2295)	338	15%
Tamoxifen (n = 2306)	437	19%

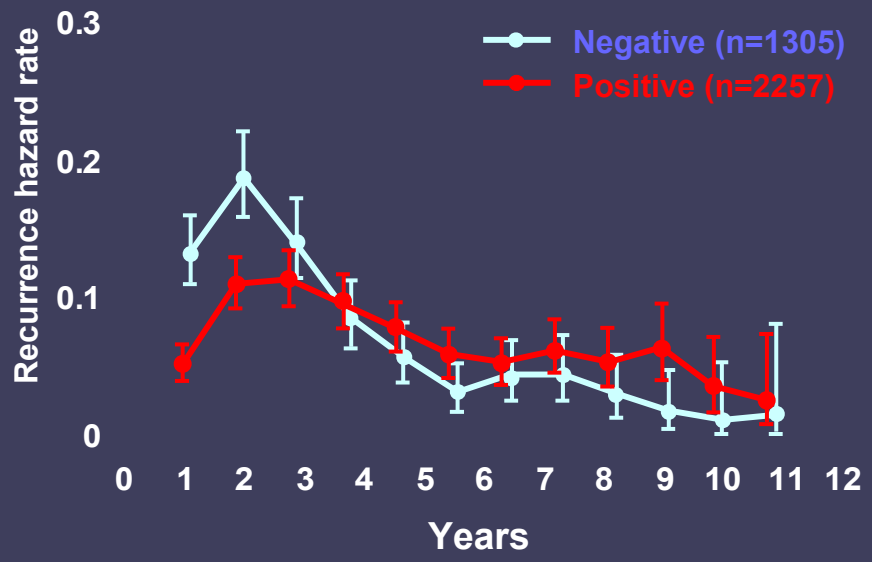
Overall Survival: 52.4 Months



荷爾蒙輔助治療及荷爾蒙延續輔助治療的分別

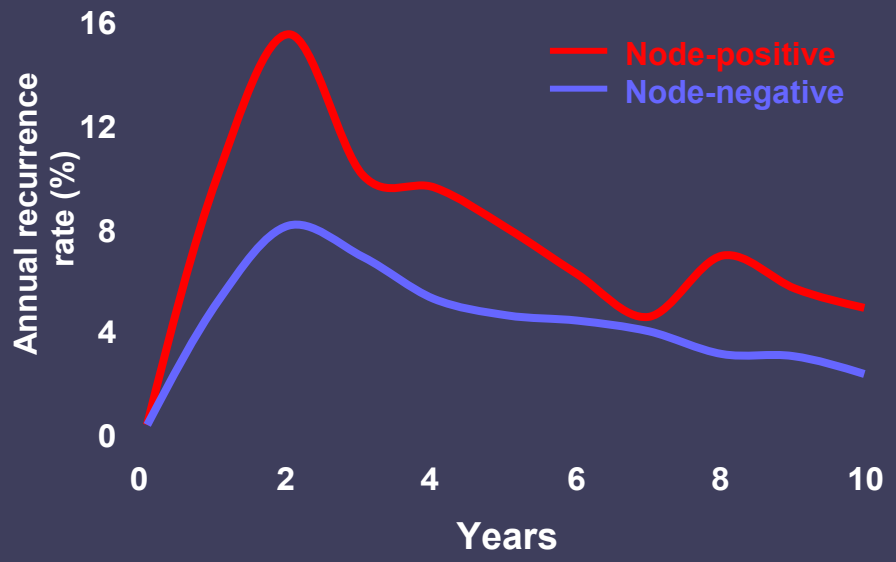
Risk of Recurrence

Annual Hazard of Recurrence by Estrogen Receptor Status



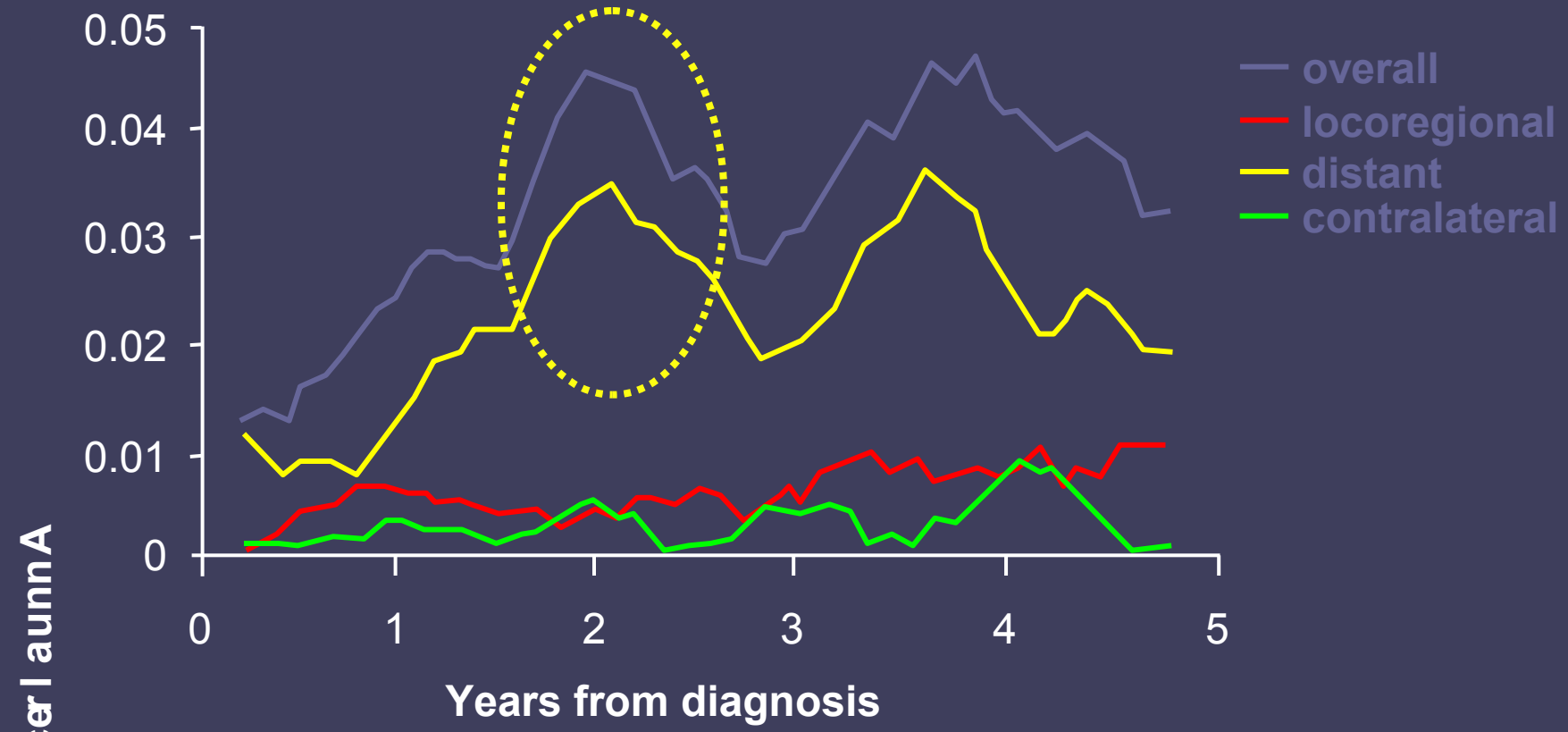
Risk of Recurrence by Nodal Status

- Untreated patients in EBCTG 1998 meta-analysis[1,2]



Saphner et al. *J Clin Oncol*. 1996;14:2738.
1. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1998;351:1451.
2. Update of Houghton. *J Clin Oncol*. 2005;23(16S):24s. Abstract 582.

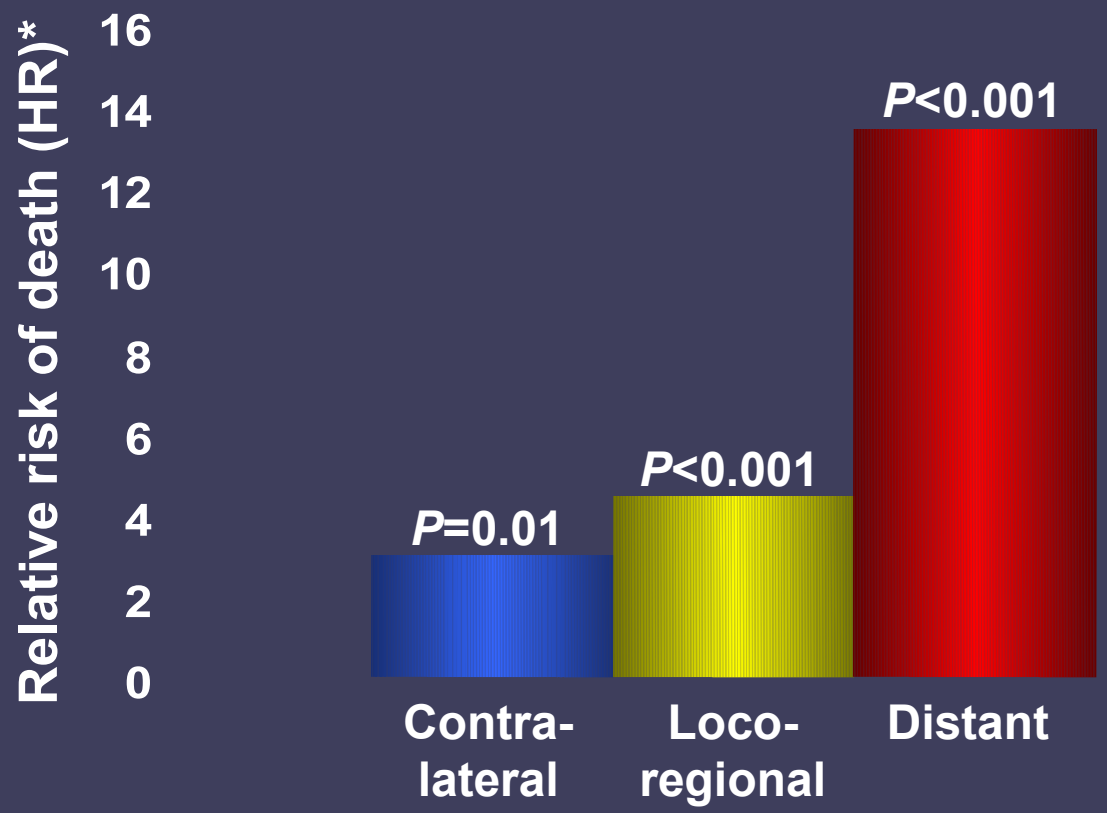
Recurrences in HR+ Breast Cancer: Distant Metastases are the Most Common



Distant recurrences are responsible for the initial peak of recurrences seen at 2 years

Mansel *et al*. *Breast Cancer Res Treat* 2006;100:(Abstract 2019).

Distant Recurrences Are Associated With the Highest Risk of Death

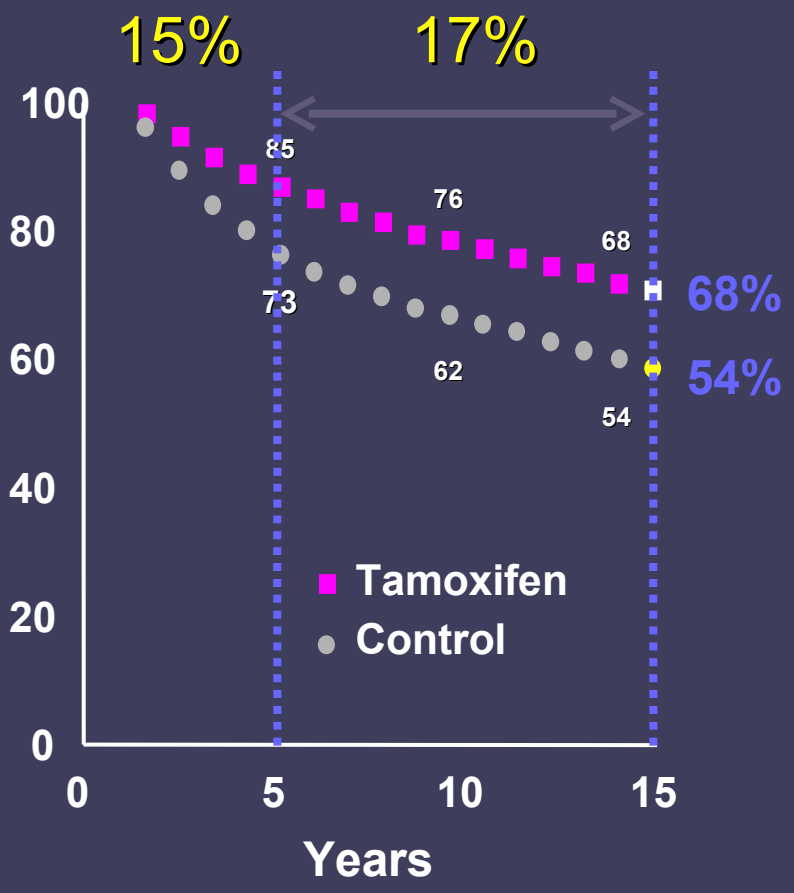


*HR (and *P* value) relative to patients with no recurrence.
HR = hazard ratio.

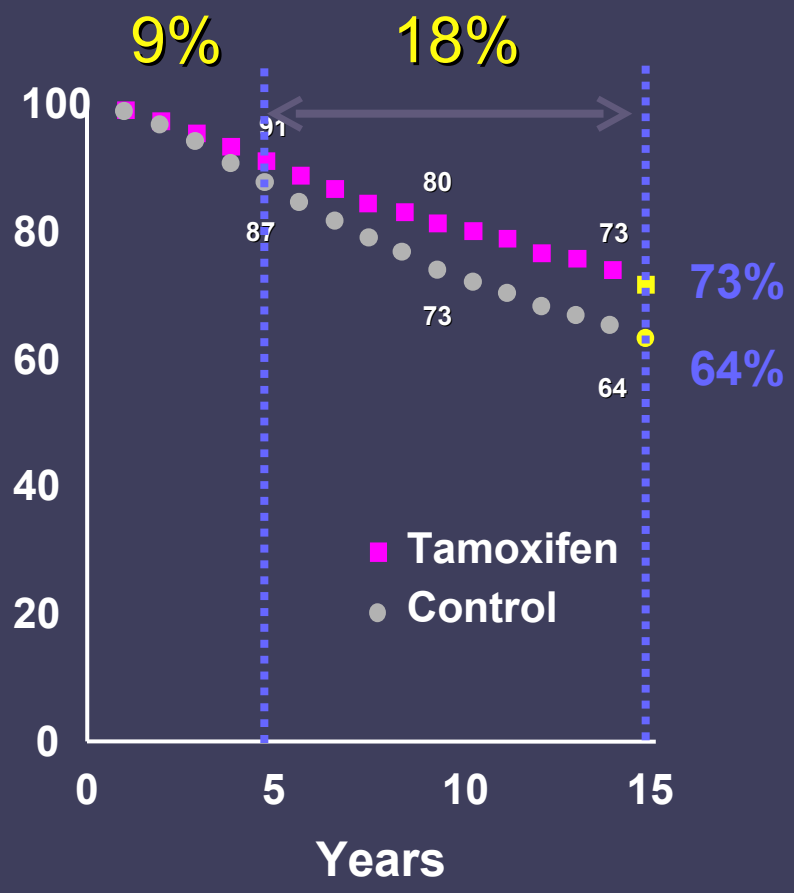
Lamerato et al. *J Clin Oncol*. 2005;23(16S):62s. Abstract 738.

Clinical Outcomes with TAM

Recurrences



Breast Cancer Deaths



Oxford Overview 2000

Can we do Better Using Antiestrogen Therapy longer than 5 Years?

NSABP-B14: JNCI 2001

ATLAS: SABCS 07

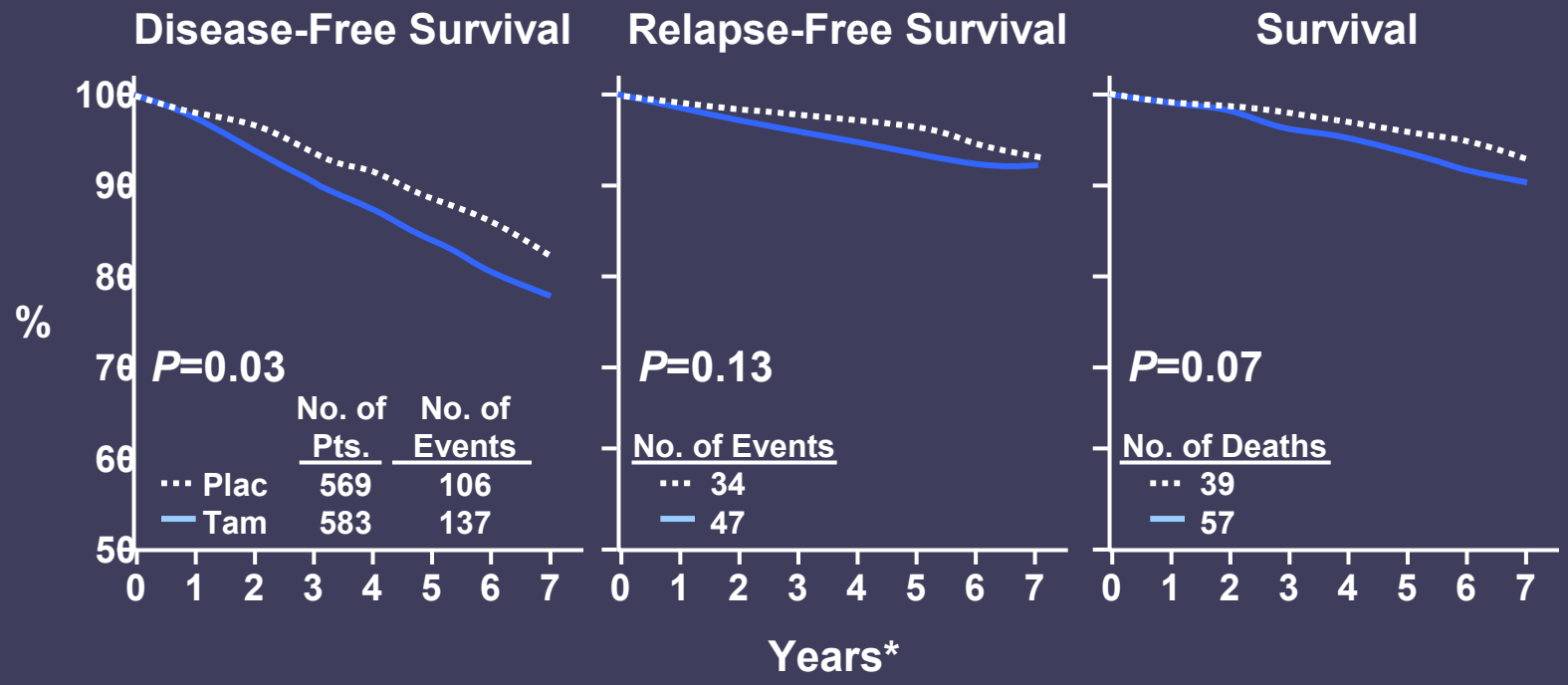
ATTOM: ASCO 08

NCI-C CTG MA.17

NSABP-B33

NSABP B-14: No Benefit of Extending TAM

After 5 years of adjuvant tamoxifen.

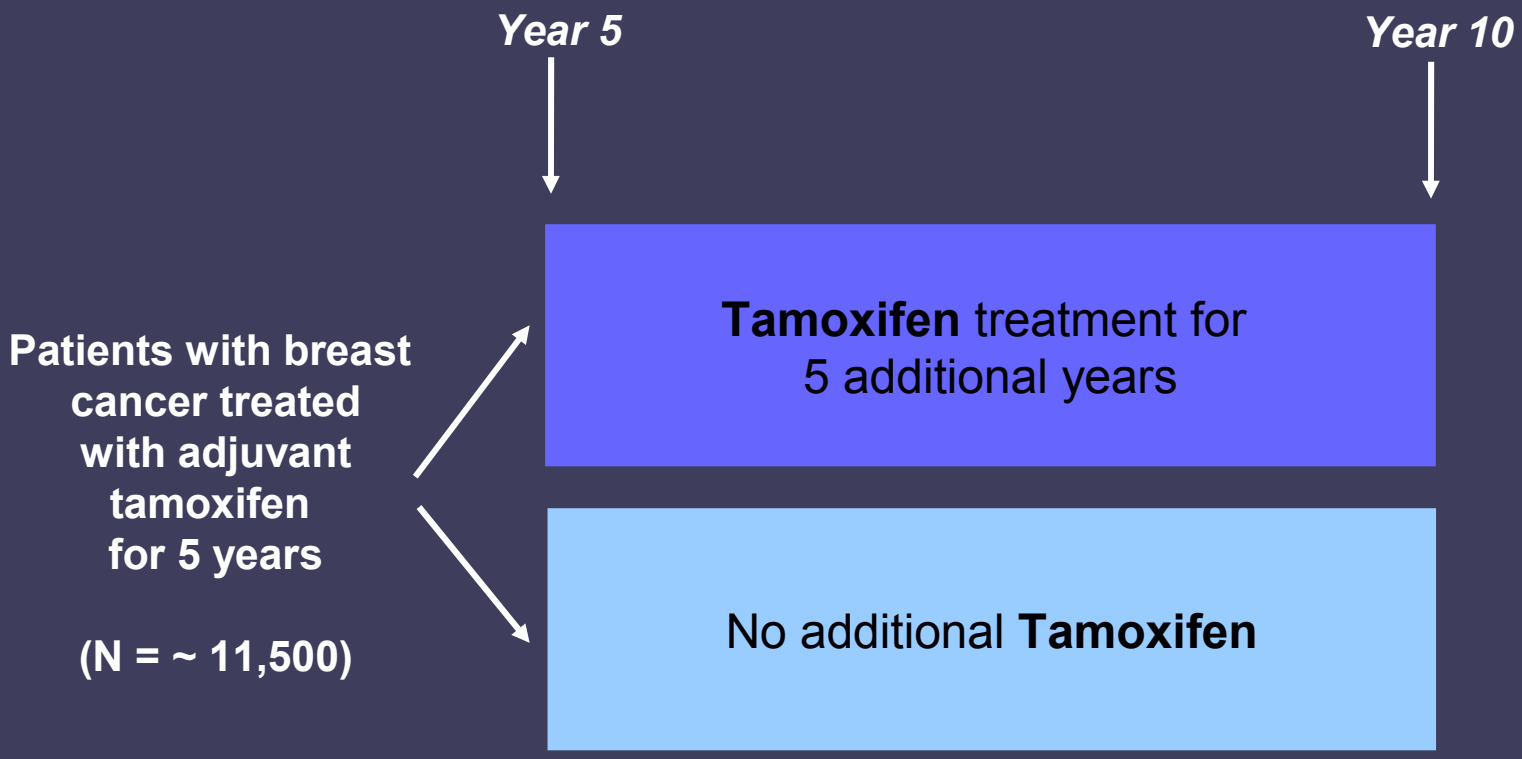


No. at risk:

···	569	531	491	229	531	491	229	554	529	257
—	583	527	472	209	527	472	209	560	528	239

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

ATLAS: Longer vs Shorter Tamoxifen in ER-Positive Breast Cancer



Annual assessments included compliance, hospital admissions, breast cancer recurrence (or new contralateral disease), other new primary cancer, and death.

Peto R, et al. SABCS 2007. Abstract 48.

Summary: ATLAS Trial

- Annual recurrence rates are approximately constant between the 2 arms both during and after the 5-year initial tamoxifen treatment period
- Recurrence rates are significantly lower among those allocated to continue tamoxifen to 10 years total
- Although breast cancer mortality was lower for those who continued tamoxifen, this was not statistically significant

Peto et al. Presented at SABCS 2007 (abstract 48)

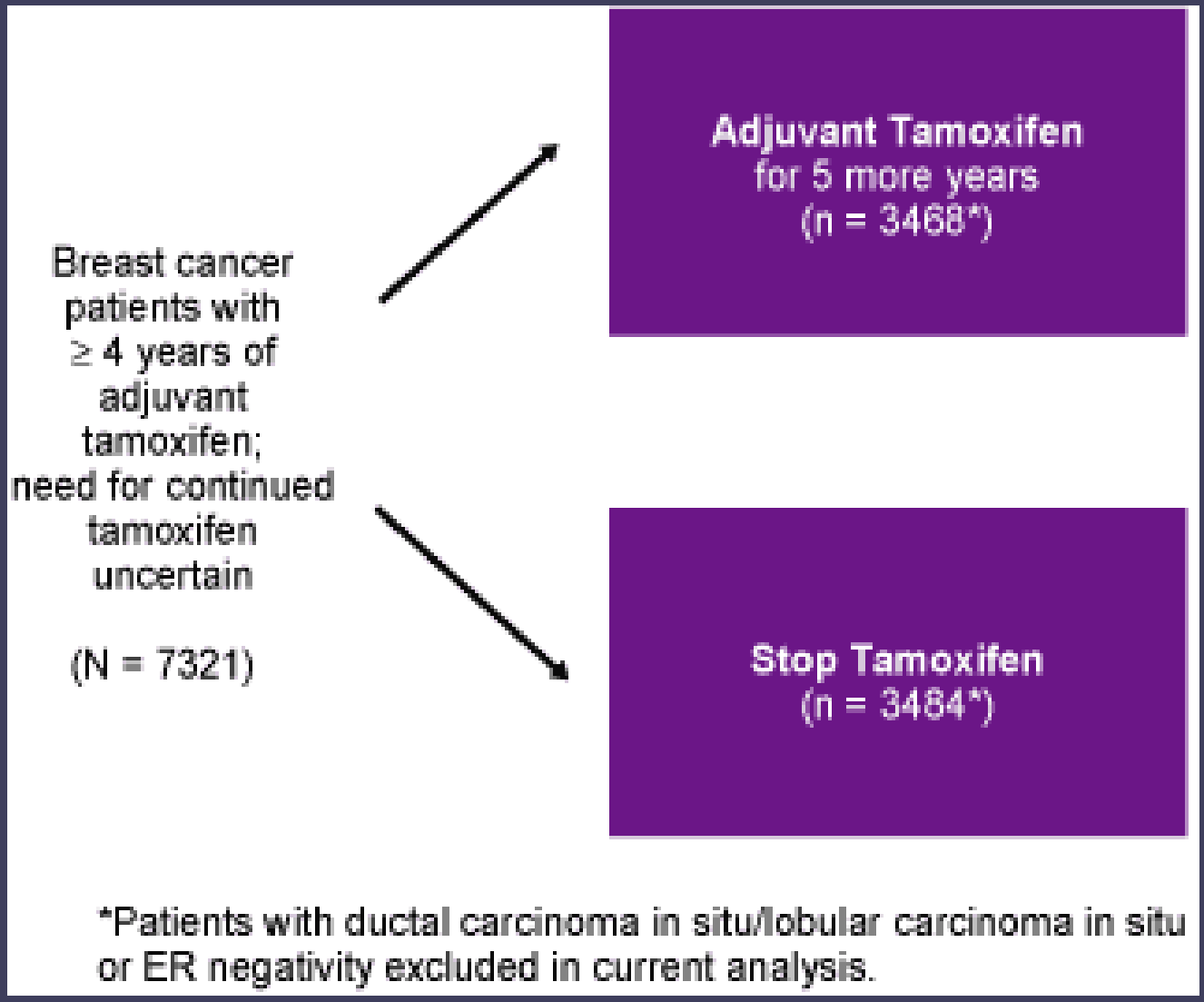
Randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6934 women with estrogen receptor-positive (ER+) of ER untested breast cancer—preliminary results

Adjuvant Tamoxifen Continued Beyond 5 Years May Not Significantly Reduce Risk of Breast Cancer Recurrence (ATTOM)

Gray RG, Rea DW, Handley K, et al. aTTom (adjuvant Tamoxifen - To offer more?)

44th American Society of Clinical Oncology Annual Meeting; 2008; Chicago, Illinois. Abstract 513.

Study Outline



Results

- Non-significant reduction in breast cancer recurrence risk in patients continuing adjuvant tamoxifen compared with patients who stopped after 5 years of adjuvant tamoxifen
  - 12.6% recurrence rate in continued tamoxifen arm vs 13.1% in treatment-stopped arm (relative risk: 0.95)
  - No expectation of strong benefit in first several years
- Increased incidence of endometrial cancer but not of related mortality

Summary 5 vs. 10 y TAM

- NSABP-B14: n=1152
- ATLAS: n=11 500
- ATTOM: n=7321

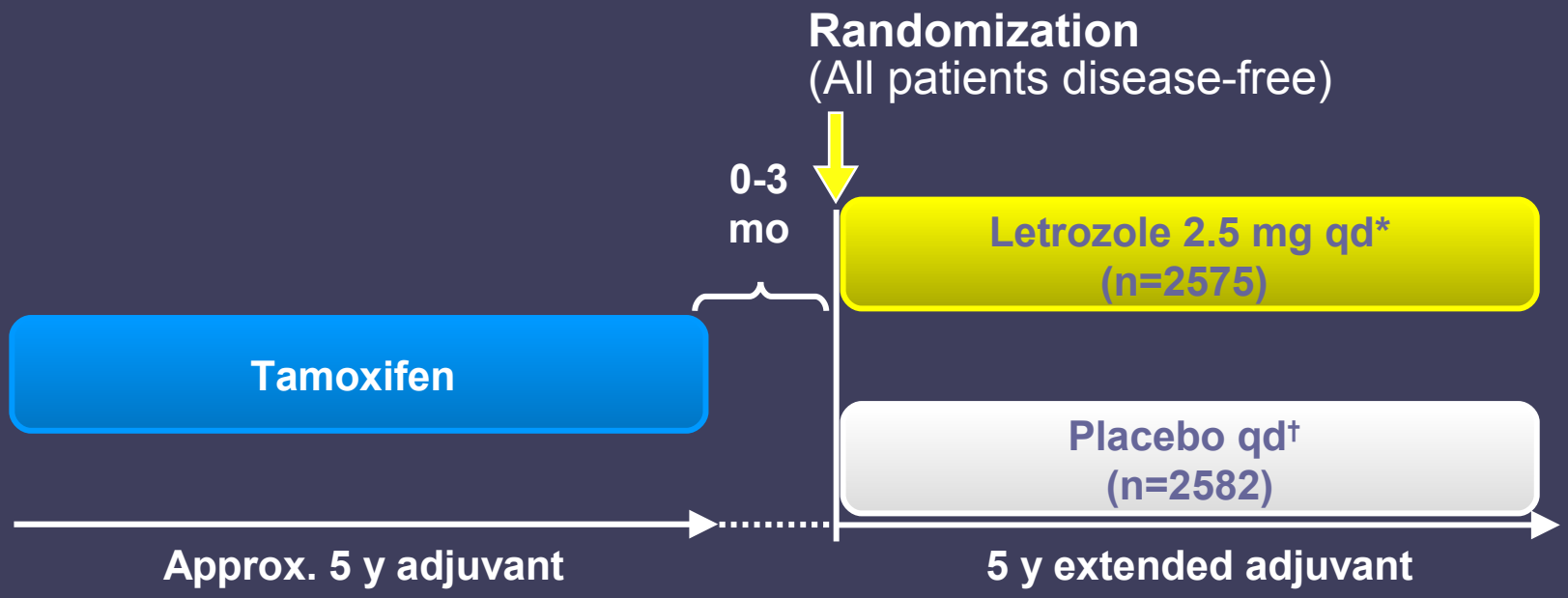
- No OS benefit; conflicting results on DFS
- Longer TAM associated with more side effects and endometrial cancers

So what about 5 years of AI after 5 years of TAM?

MA.17

B-33

NCIC CTG MA.17: Trial Design



Primary end point: DFS
Secondary end points: OS, cBC, safety, QOL
Substudies: BMD/bone markers, lipid profile

*n=2575 (efficacy), 2154 (safety).
†n=2582 (efficacy), 2145 (safety).
NCIC CTG = National Cancer Institute of Canada Clinical Trials Group; QOL = quality of life; BMD = bone mineral density.

Goss et al. *N Engl J Med*. 2003;349:1793.
Goss et al. *J Natl Cancer Inst*. 2005;97:1262.

MA.17: Key Efficacy Results

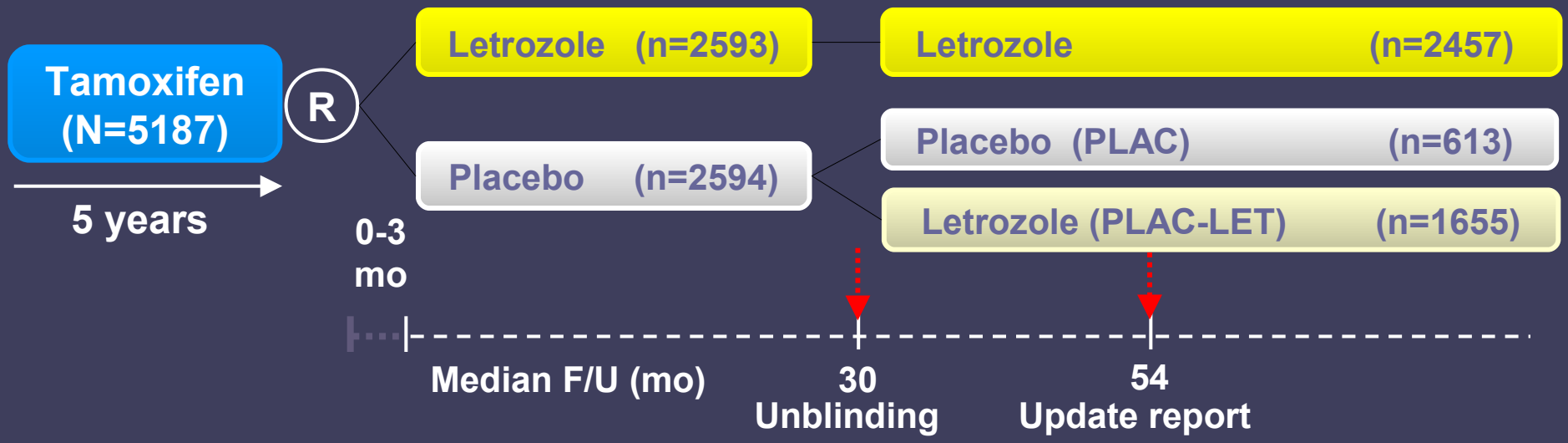
	HR (95% CI)		
	DFS	**Distant DFS**	**OS**
Node+ pts	0.61* (0.38-0.98)	0.53* (0.36-0.78)	0.61* (0.38-0.98)
Overall	**0.58* (0.45-0.76)**	**0.60* (0.43-0.84)**	**0.82 (0.57-1.19)**
Node– pts	0.45* (0.27-0.73)	0.63 (0.31-1.27)	1.52 (0.76-3.06)

- Similar reduction in local recurrences, new primaries, and distant recurrences occurred in node+ and node– patients

*Significant improvement with letrozole vs placebo.

Goss et al. *J Natl Cancer Inst*. 2005;97:1262.
Update of Goss et al. *Proc Am Soc Clin Oncol.* 2004;23:87. Abstract 847.

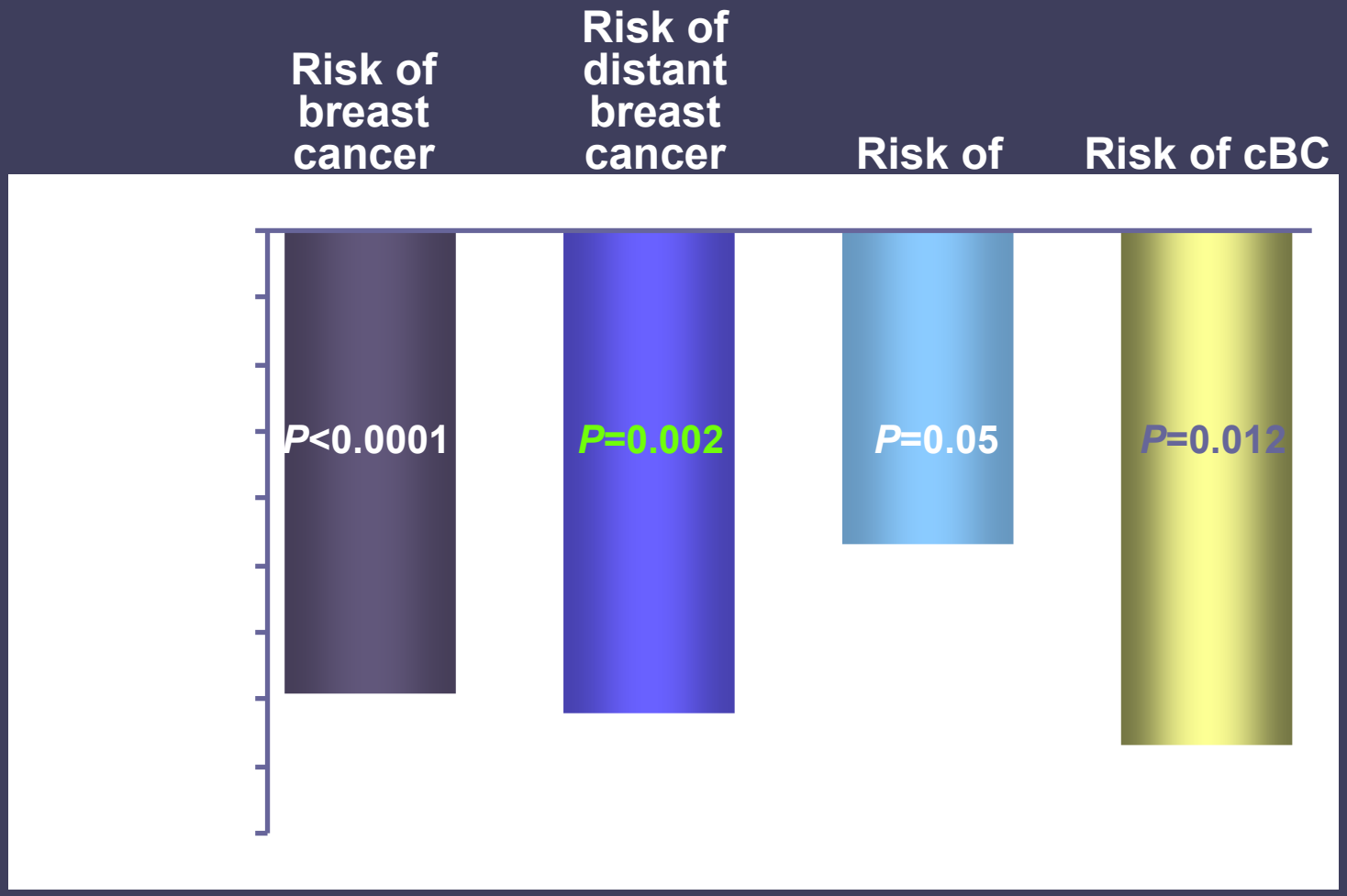
MA.17: Post-Unblinding Analysis—Design and Patients



- Purpose: compare PLAC-LET vs PLAC for benefits/safety of starting letrozole after prolonged periods (1-5 y) off tamoxifen
- Post-unblinding groups differed in baseline characteristics, but PLAC-LET patients had higher risk of recurrence; due to imbalance, multivariate analysis including key variables was undertaken
- Subgroup analyses included nodal status and prior chemotherapy

Update of Goss et al. *Breast Cancer Res Treat.* 2005;94(suppl 1):S10. Abstract 16.
Update of Robert et al. *J Clin Oncol.* 2006;24(18S):15s. Abstract 550.

MA.17: Post-Unblinding Analysis—Efficacy Outcomes

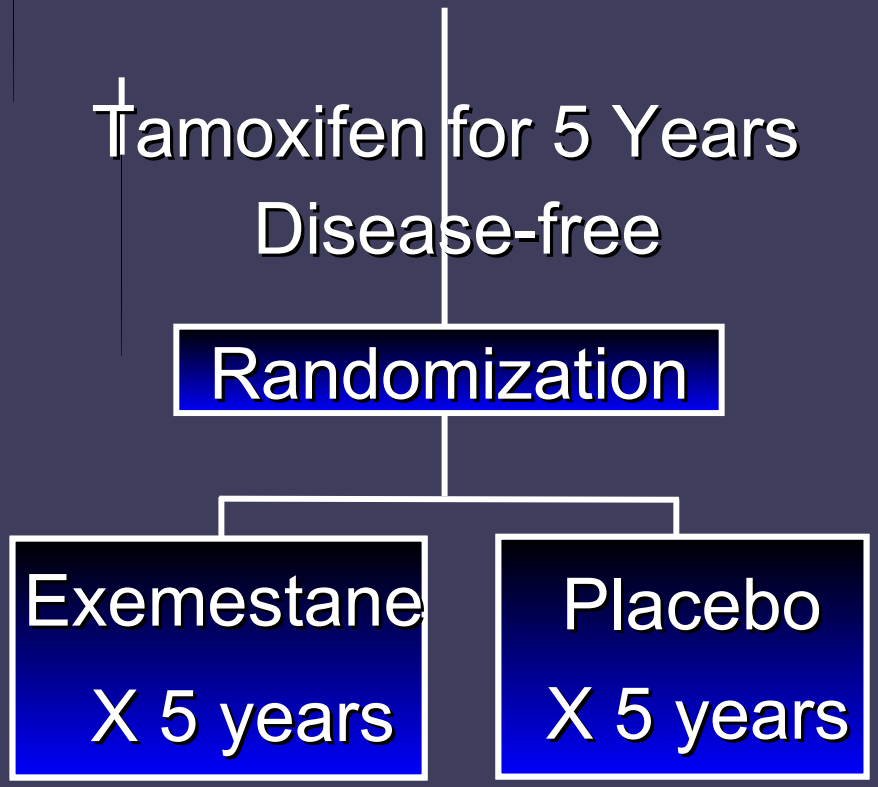


Update of Goss et al. *Breast Cancer Res Treat.* 2005;94(suppl 1):S10. Abstract 16.
Update of Robert et al. *J Clin Oncol.* 2006;24(18S):15s. Abstract 550.

NSABP B-33 Trial

Stage I-II Breast Cancer
Postmenopausal, ER or PgR-Positive

Tamoxifen for 5 Years
Disease-free



Protocol Amendment in 2002

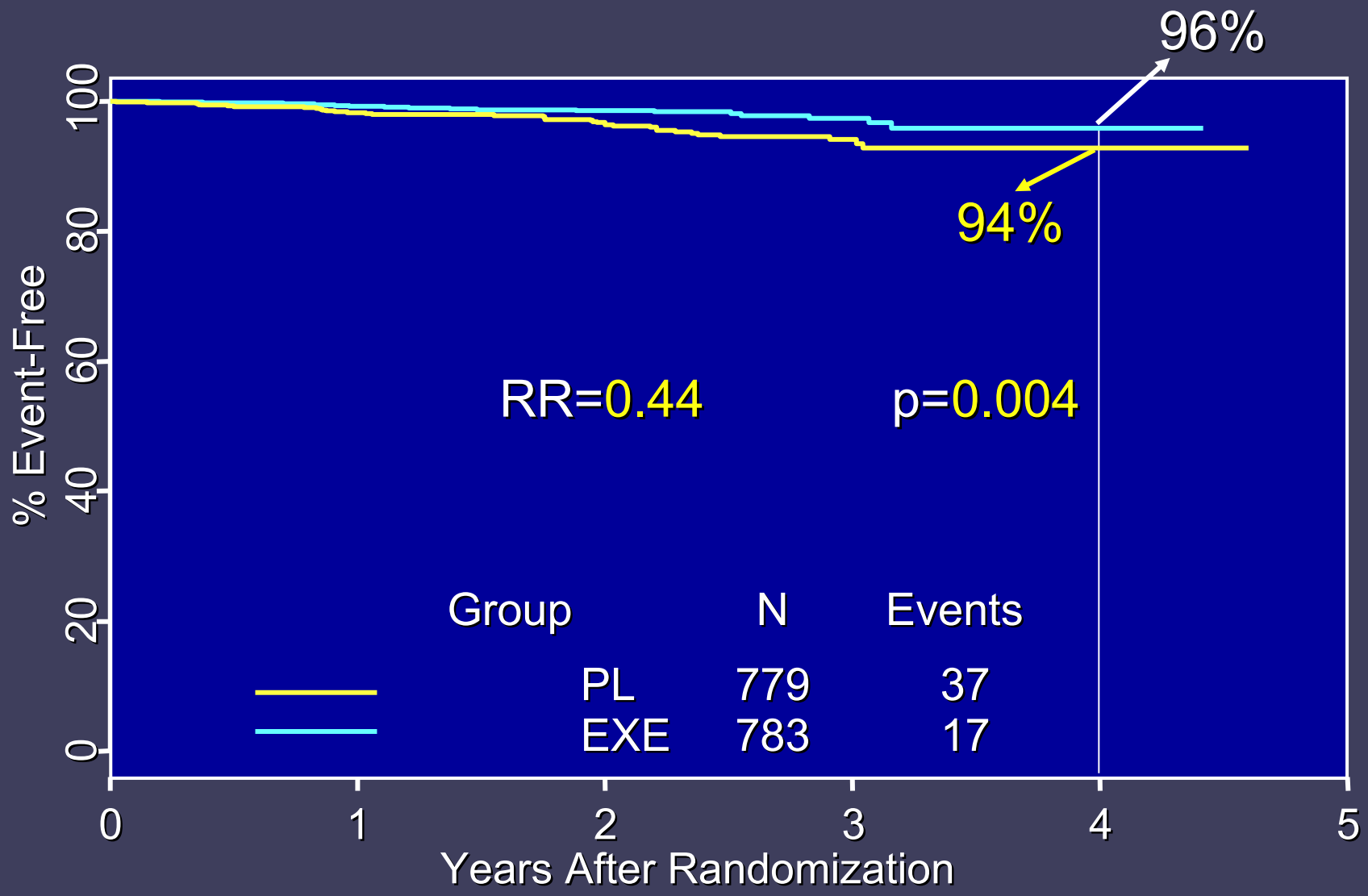
荷爾蒙輔助治療副作用
(Side effect)

B-33: Accrual

Opened:	May, 1 2001
Target Accrual:	3000 pts
Accrual in 10/03:	1598 pts

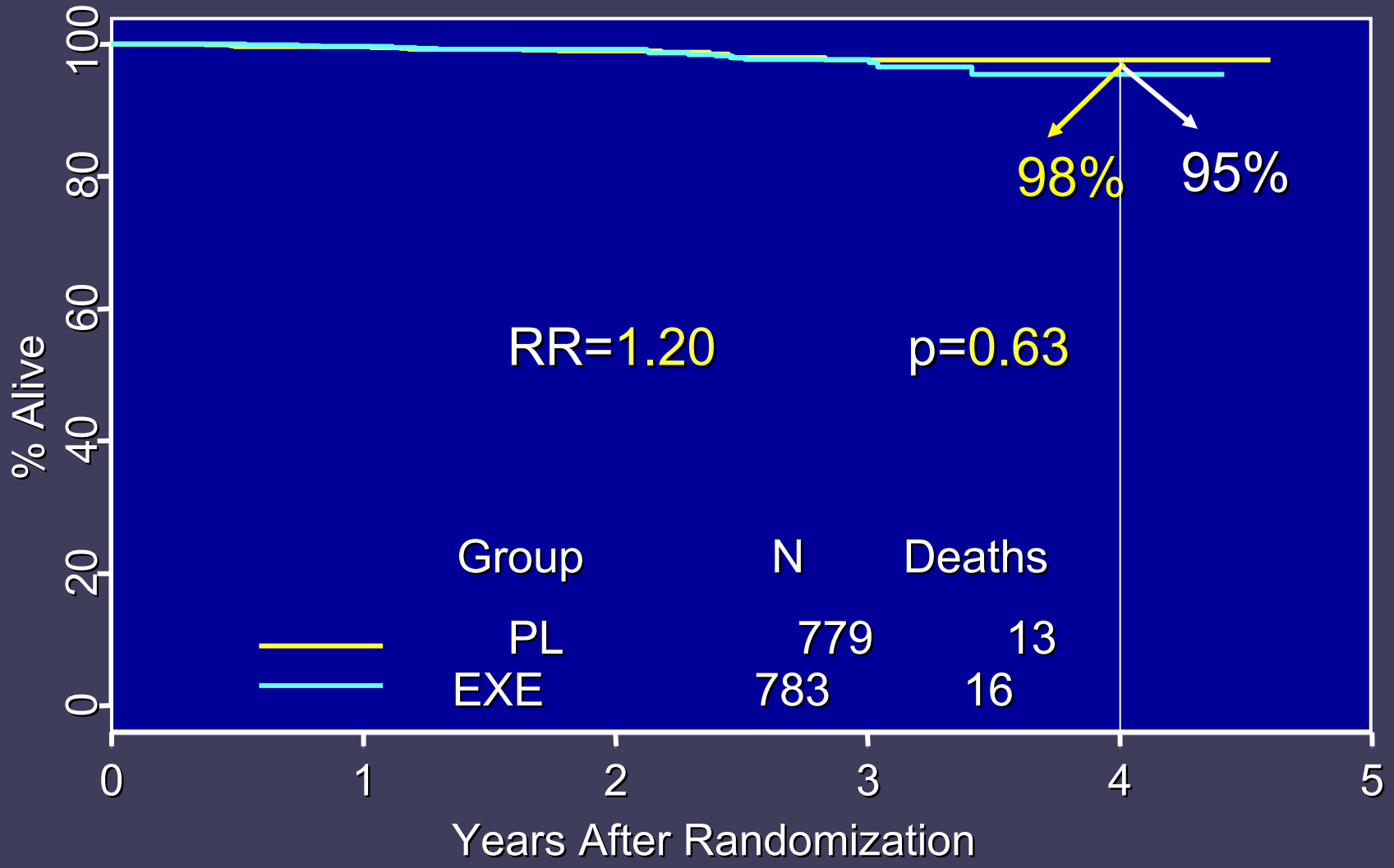
Accrual stopped in October 2003 after disclosure of results from the NCIC MA.17 trial

B-33: Relapse-Free Survival*



*Eligible pts with follow-up

B-33: Overall Survival*



*Eligible pts with follow-up

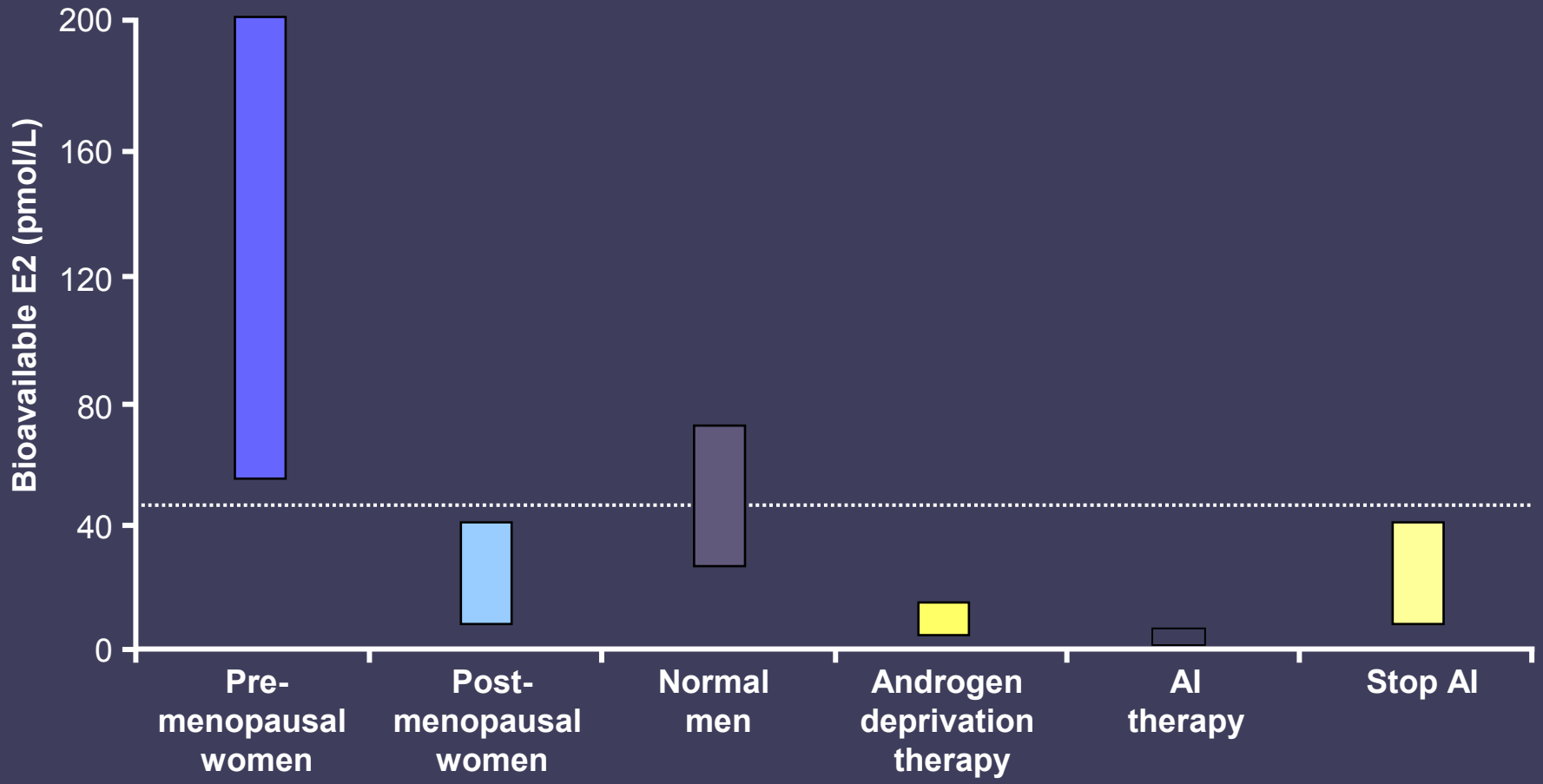
Summary

- The use of AIs is clearly indicated in early breast cancer - postmenopausal women
- Outcomes (DFS, RFS, even OS) are better
- Effective when used upfront, after 2-3 years of TAM (the strategy with significantly better OS benefit!), or even after 5 years of TAM in high risk (LN+)
- Different risk categories and side effect profiles will drive the decision on how to proceed
- There is no “best” for all patients; individual discussion and decision is the “best” approach
- Duration: definitely not only 5 years, maybe 15 years or even longer? But TAM not longer than 2 – 5 years

Adverse Effects and Toxicity of Endocrine Therapies

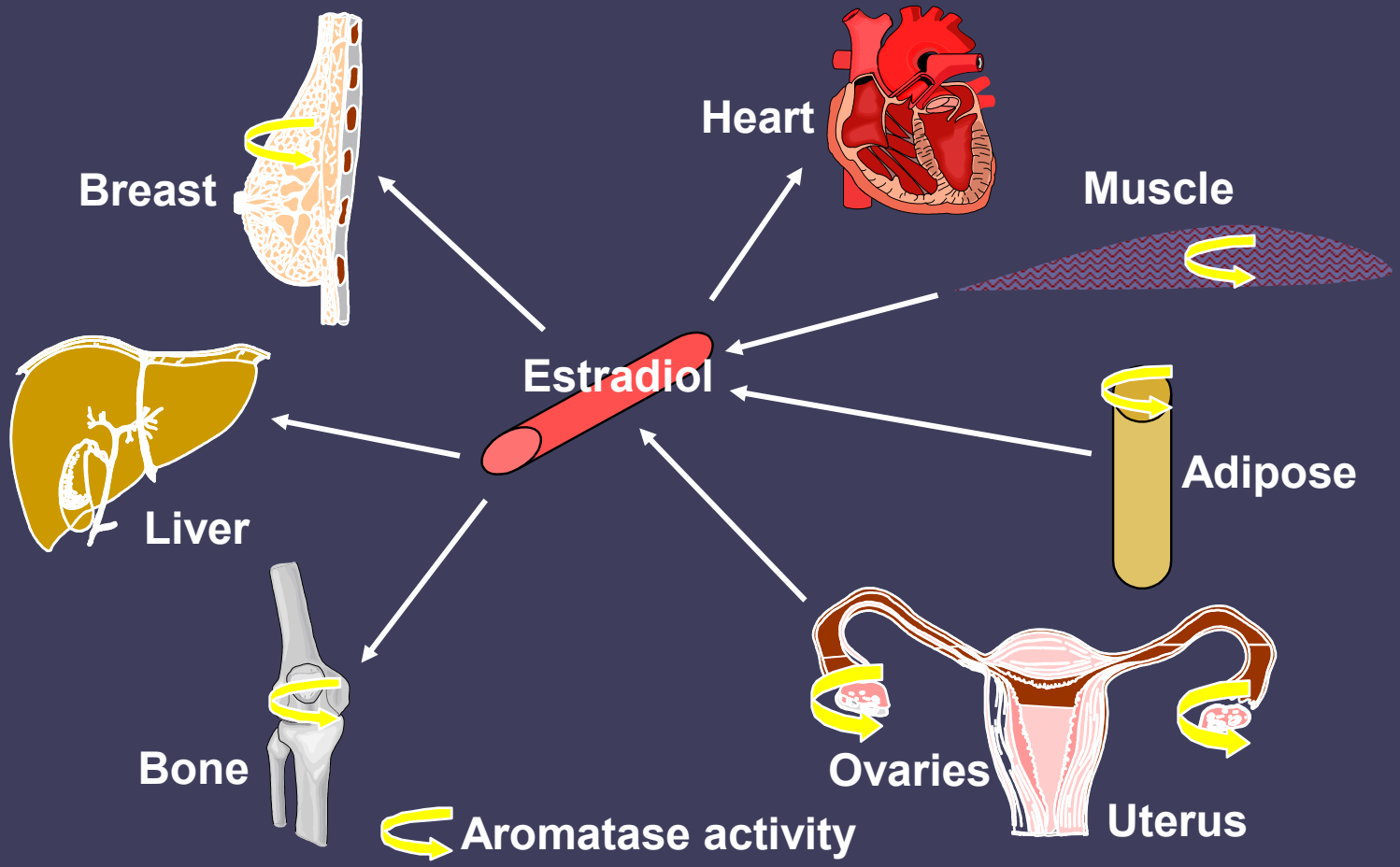
- Antagonizing estrogen is a key strategy in the treatment and prevention of breast cancer
- Current adjuvant therapies in ER-positive postmenopausal breast cancer
  - Tamoxifen
  - AIs
- Toxicity and end-organ effects of endocrine therapies
  - Tamoxifen is a mixed agonist/antagonist
  - AIs profoundly suppress plasma and tissue estrogen levels

Estrogen Levels in Women and Men



Adapted from Khosla S, et al. J Clin Endocrinol Metab. 2001;86:3555-3561.

Estrogen Synthesis and Tissue-Specific Effects

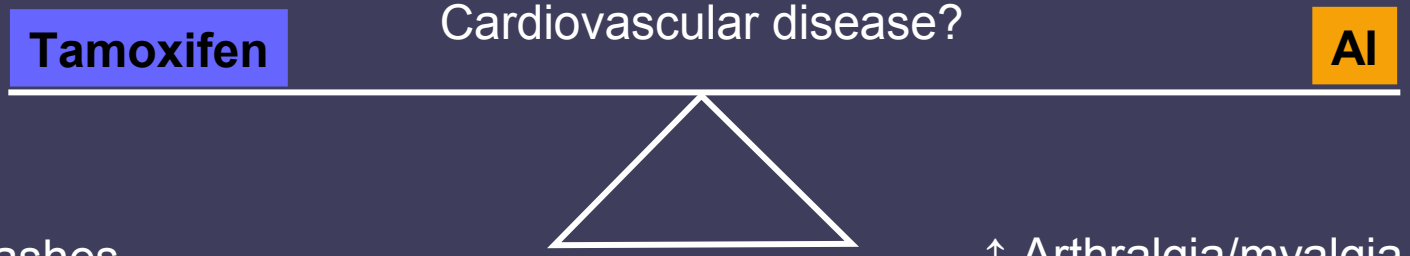


AIs and Tamoxifen: Potential Risks and Benefits

↓ Contralateral BC
↓ Osteoporosis risk
↓ Myalgia
↓ Hyperlipidemia

↓ Contralateral BC
↓ Deep vein thrombosis
↓ Endometrial cancer
↓ Hot flashes

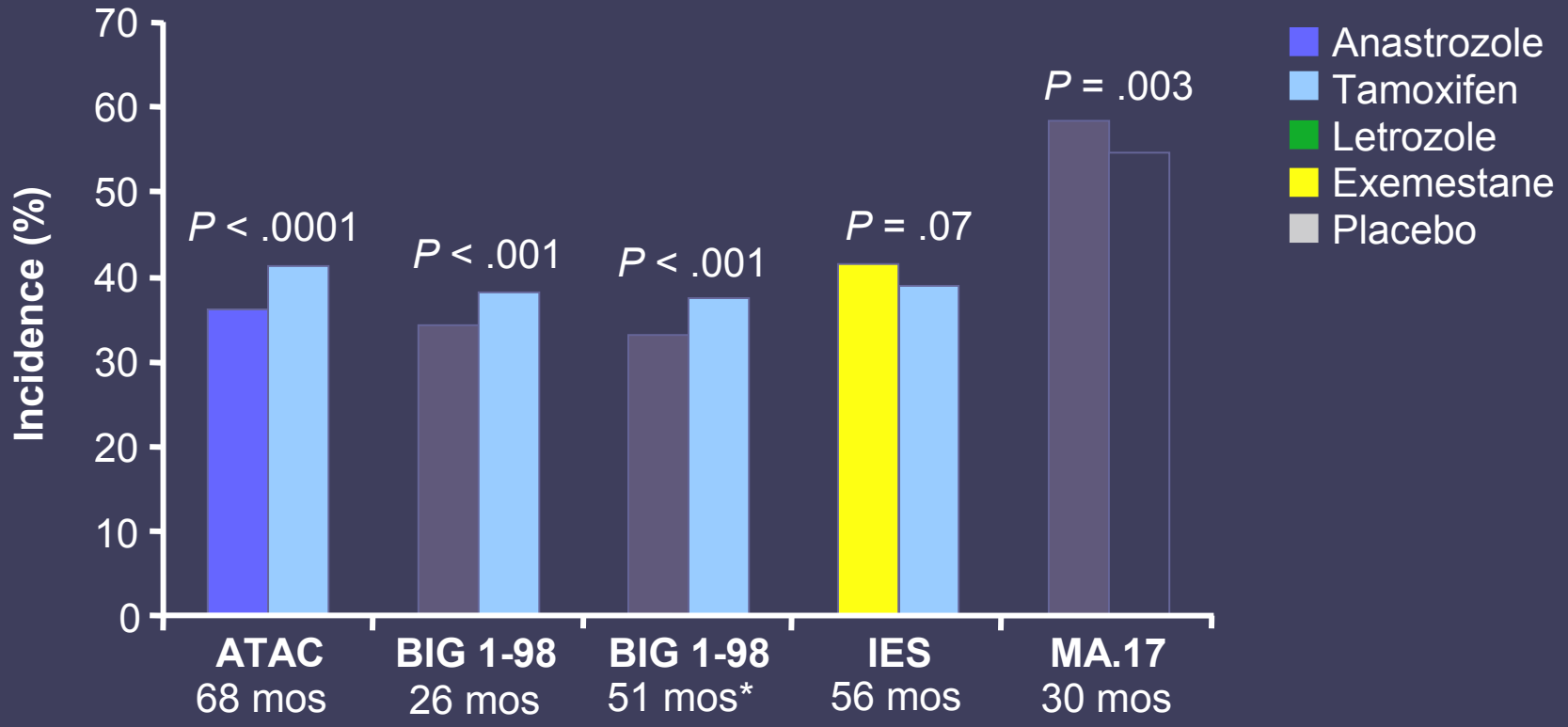
Neurocognition?
Sexual function?
Cardiovascular disease?



↑ Hot flashes
↑ Thromboemboli
↑ Endometrial cancer
↑ Genitourinary adverse effects

↑ Arthralgia/myalgia
↑ Osteoporosis risk

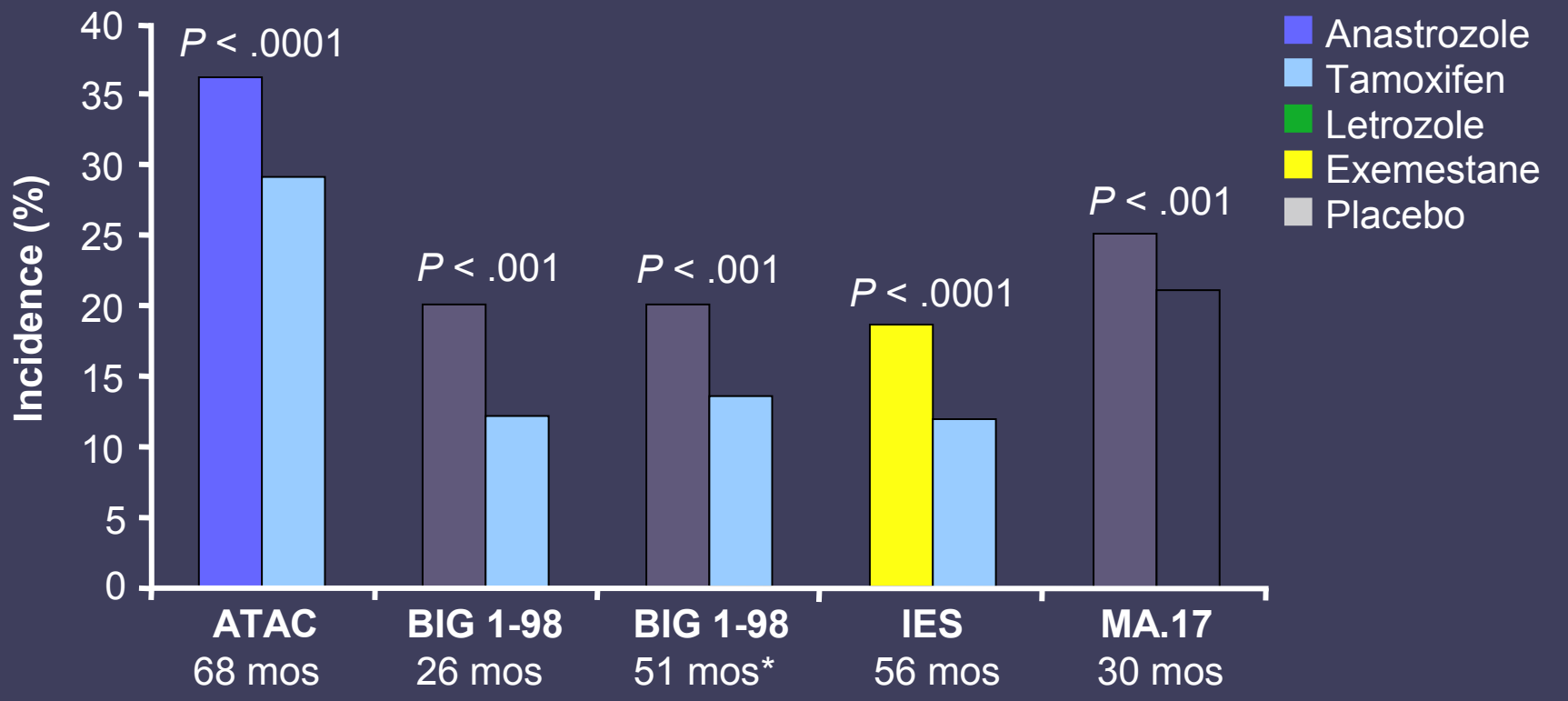
Hot Flashes（潮熱）in Adjuvant AI Trials



*51-month analysis restricted to monotherapy arms.

ATAC Trialists' Group. Lancet. 2005;365:360. Thurlimann B, et al. N Engl J Med. 2005;353:2747-2757. Coates AS, et al. J Clin Oncol. 2007;25:486-492. Coombes RC, et al. Lancet. 2007;369:559-570. Goss PE, et al. J Natl Cancer Inst. 2005;97:1262-1271.

Arthralgia（關節痛）in Adjuvant AI Trials



*51-mo analysis restricted to monotherapy arms.

ATAC Trialists' Group. Lancet. 2005;365:360. Coates AS, et al. J Clin Oncol. 2007;25:486-492. Coombes RC, et al. Lancet. 2007;369:559-570. Goss PE, et al. J Natl Cancer Inst. 2005;97:1262-1271.

Treatment of Arthralgia

- Assess and monitor arthralgia before and during AI therapy
  - Mild increase of symptoms
    - Exercise, weight reduction
- Moderate to severe increase of symptoms
  - If eligible for NSAIDs
    - High dose NSAID or “coxib”
    - NSAID plus paracetamol
    - NSAID plus codeine phosphate
  - If NSAIDs are contraindicated
    - High dose co-codamol*
  - If no relief of symptoms achievable
    - Switch to another (nonsteroidal) AI

	Daily Dose
Paracetamol	4000 mg (8 x 500 mg/day)
Ibuprofen	1600-2400 mg (4 x 600 mg/day)
Diclofenac	150 mg (3 x 50 mg/day)
Naproxen	1000 mg (2 x 500 mg/day)
Celecoxib	400 mg (2 x 100-200/day)
Etoricoxib	60 mg (1 x 60 mg/day)

*Codeine phosphate plus paracetamol.

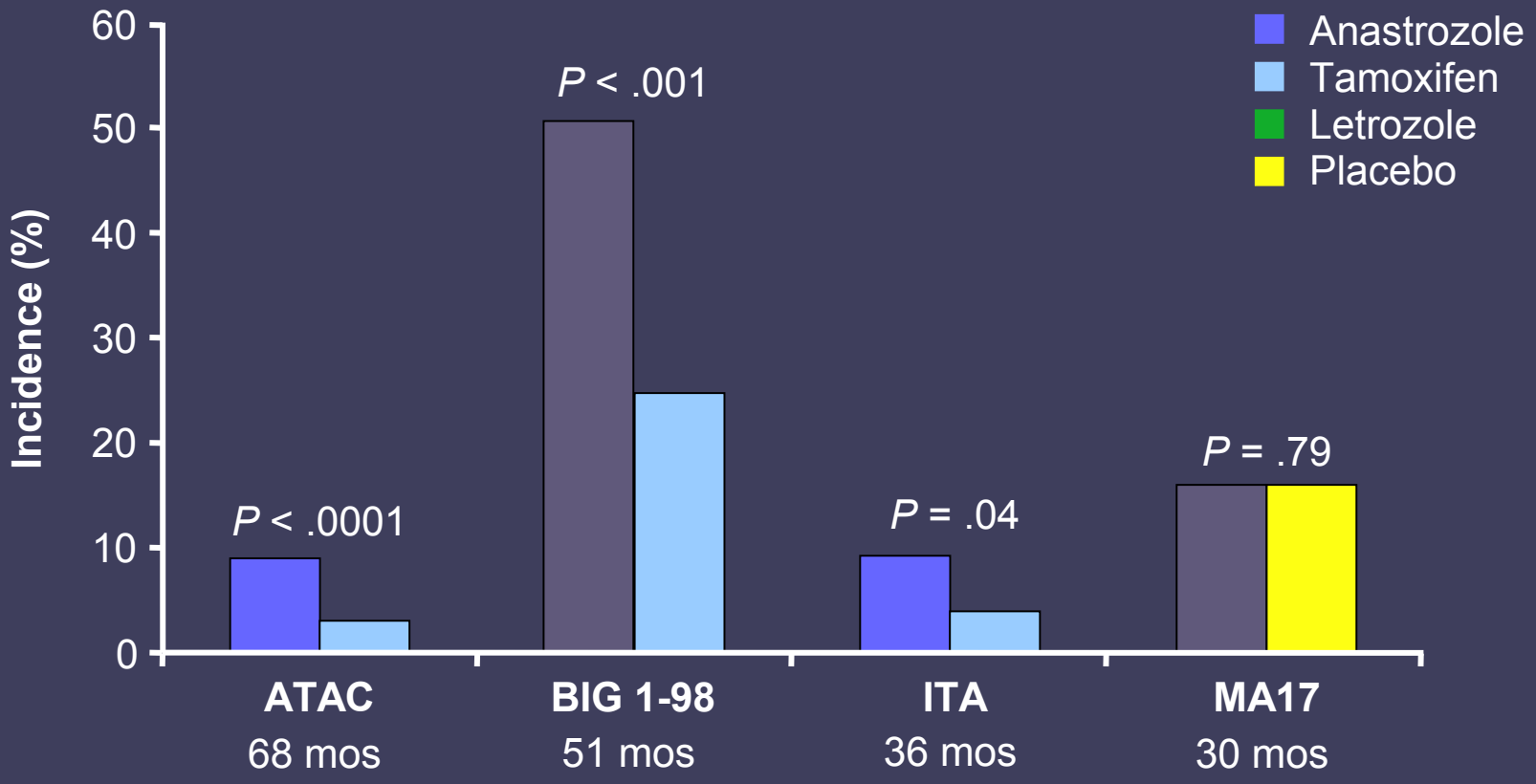
Thrombosis in Adjuvant AI trials

Study	Follow-up, mos	AI	Reference Drug	Event	AI vs Reference, %	*P* Value
ATAC	68	Anastrozole	Tamoxifen	Venous Deep venous	2.8 vs 4.5 1.6 vs 2.4	.0004 .02
BIG 1-98	26	Letrozole	Tamoxifen	Thromboembolic	1.0 vs 2.4 (2.0 vs 3.8*)	< .001
IES	56	Exemestane	Tamoxifen	Thromboembolic	1.2 vs 2.3	.004
ARNO	26	Anastrozole	Tamoxifen		NR	
MA-17	30	Letrozole	Placebo		0.4 vs 0.2	NR

*51-mo analysis restricted to monotherapy arms.

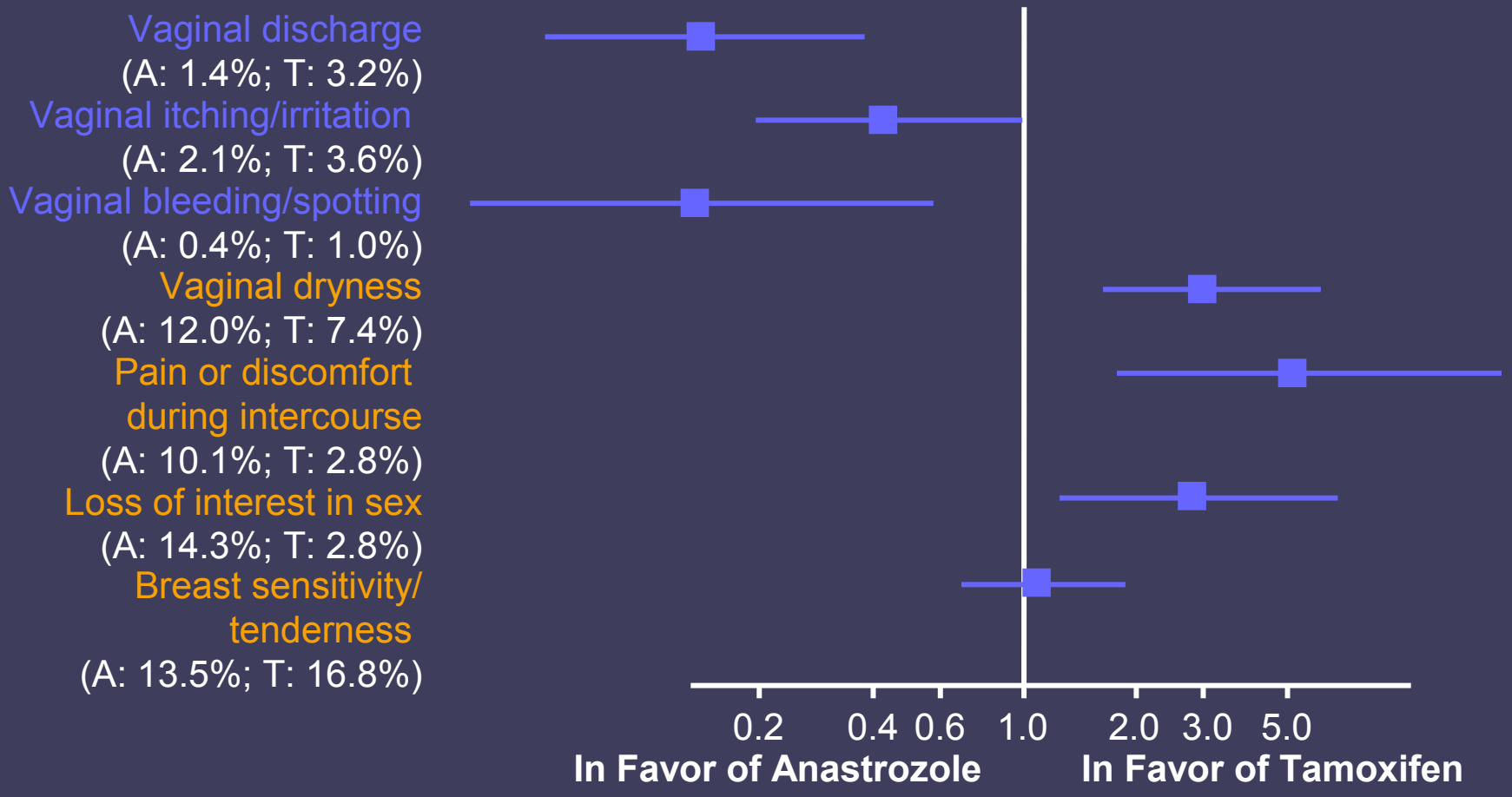
ATAC Trialists' Group. Lancet. 2005;365:360. Thurlimann B, et al. Eur J. Cancer 2003;39:2310-2317. Thurlimann B, et al. N Engl J Med. 2005;353:2747-2757. Coates AS, et al. ESMO 2006. At: http://www.ibcsg.org/public/documents/pdf/trial_18-98_big1-98/BIG1-98_ESMO_2006.pdf. Coombes RC, et al. J Clin Oncol. 2006;24(18S):933s. Abstract LBA527. Jakesz et al. Breast Cancer Res Treat. 2004;88:57. Abstract 2. Goss PE, et al. J Natl Cancer Inst. 2005;97:1262-1271.

Hypercholesterolemia（高膽固醇）or Lipid Disorders in Adjuvant AI Trials



Buzdar A, et al. Lancet Oncol. 2006;7:633-643. Coates AS, et al. J Clin Oncol. 2007;25:486-492. Boccardo F, et al. J Clin Oncol. 2005;23:5138-5147. Goss PE, et al. J Natl Cancer Inst. 2005;97:1262-1271.

ATAC Gynecologic Symptoms (婦科病徵) at 3 Months



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

ATAC Diagnosis Leading to Hysterectomy（婦科病徴）

	Anastrozole, n (%) (N = 2229)*	Tamoxifen, n (%) (N = 2236)*
Malignancy	7 (0.3)	20 (0.9)
Benign	23 (1.0)	95 (4.2)
▪ Prolapse	7 (0.3)	32 (1.4)
▪ Fibroids	8 (0.4)	15 (0.7)
▪ Polyps	1 (< 0.1)	14 (0.6)
▪ Ovarian cysts	2 (0.1)	4 (0.2)
▪ Other	5 (0.2)	30 (1.3)

*Patients with an intact uterus at baseline.

Duffy S, et al. BJOG. 2003;110:1099-1106.

AIs Gynecologic and Endometrial Effects（婦科病徵）

- AIs lower serum estradiol and have a negative effect on the endometrium
- AIs cause fewer benign and malignant gynecologic problems compared with tamoxifen ($P < .0001$)
- Tamoxifen associated with > 4 times hysterectomy incidence compared with AIs ($P < .0001$)
- Women posttamoxifen have less vaginal bleeding and fewer endometrial cancers compared with placebo patients

Duffy S, et al. BJOG. 2003;110:1099-1106.

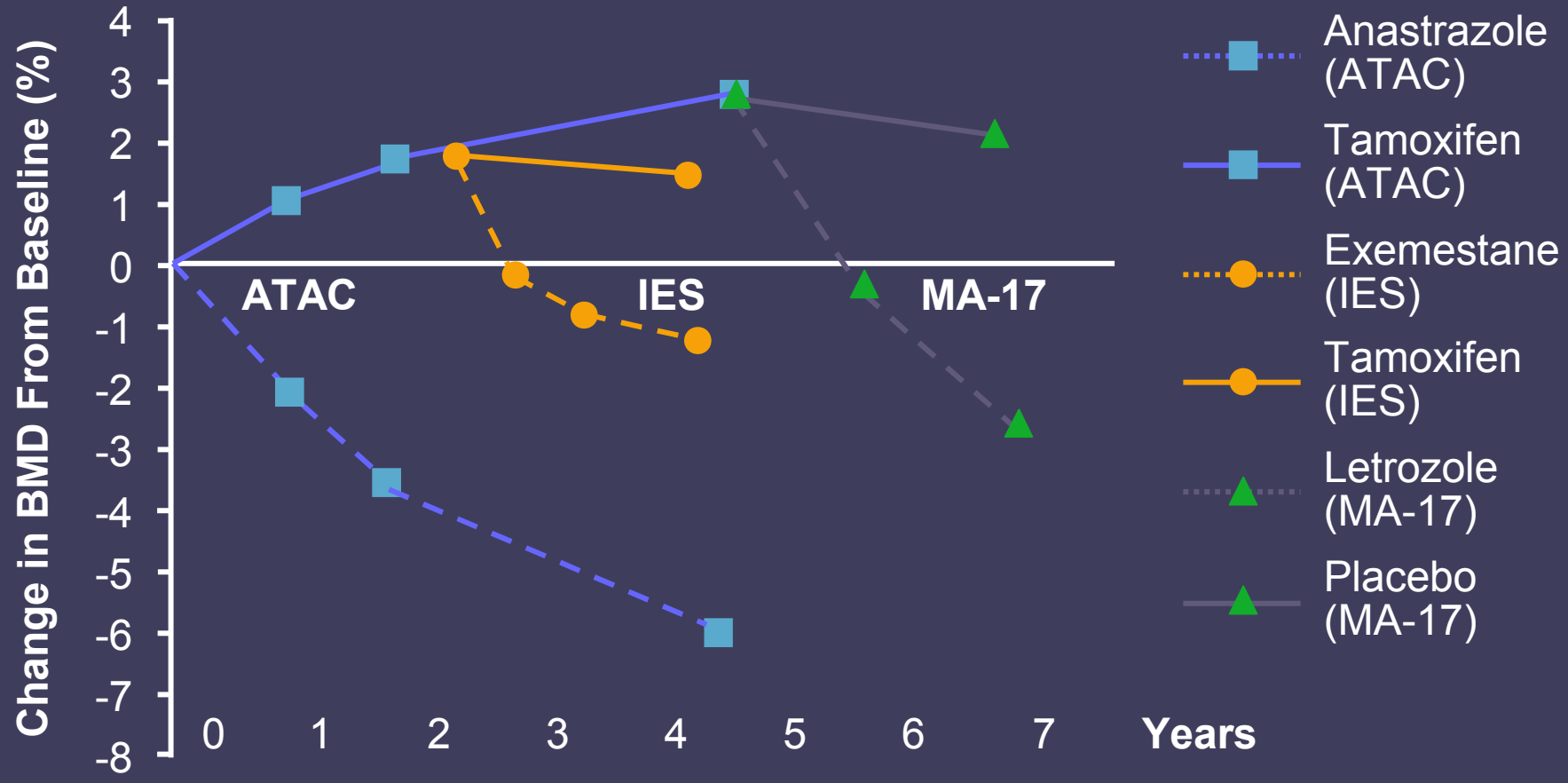
AIs Effects on Bone Metabolism（骨骼健康）

- Bone remodeling is a “coupled” process of bone resorption followed by bone formation
- Tamoxifen’s estrogen agonist action reduces clinical fracture risk during but not after treatment
- Reduction of estrogen by AIs increases bone resorption
- The steroidal AI exemestane and its principal metabolite are androgenic

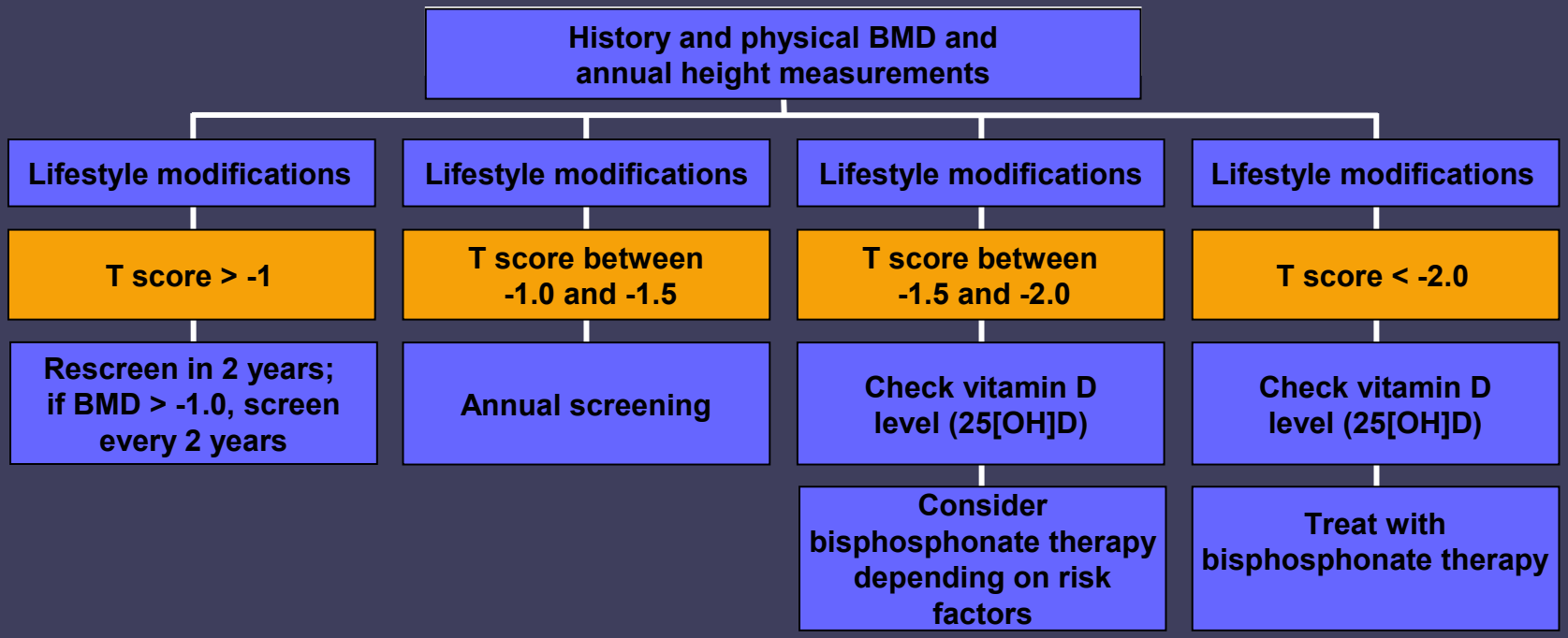
Fracture Rates in Adjuvant AI Trials（骨骼健康）

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

Influence of Different AI Strategies on BMD



Bone Management Strategies for Patients Taking AIs



In addition to monitoring changes in BMD, any changes in height or complaints of back pain should prompt the oncologist to obtain a lateral thoracic and lumbar x-ray of the spine to determine if vertebral fractures are present. If so, the patient should be referred to a bone health specialist.

Chien AJ, et al. J Clin Oncol. 2006;24:5305-5312. Goss P, et al. American Journal of Oncology Review. 2006;5(suppl 1):35-43.

荷爾蒙輔助治療的最新發展

Recommendation regarding the Use of AI in the adjuvant setting

- Preferred sequential than concurrent with chemotherapy
- Clear preference of switching from TAM to AI after 2 – 3 years
- Consider AI upfront
  - High risk
  - HER2 positive
  - Those who take SSRI

Recommendation regarding the Use of AI in the adjuvant setting

- Not to use 5 years of TAM upfront in postmenopausal patient
- Addition of AI after 5 y of TAM in LN+ patient
- Check ovarian function in younger postmenopausal patient
- Check BMD prior to starting AI
- Use Vitamin D and Calcium
- No AI in pre-menopausal patient

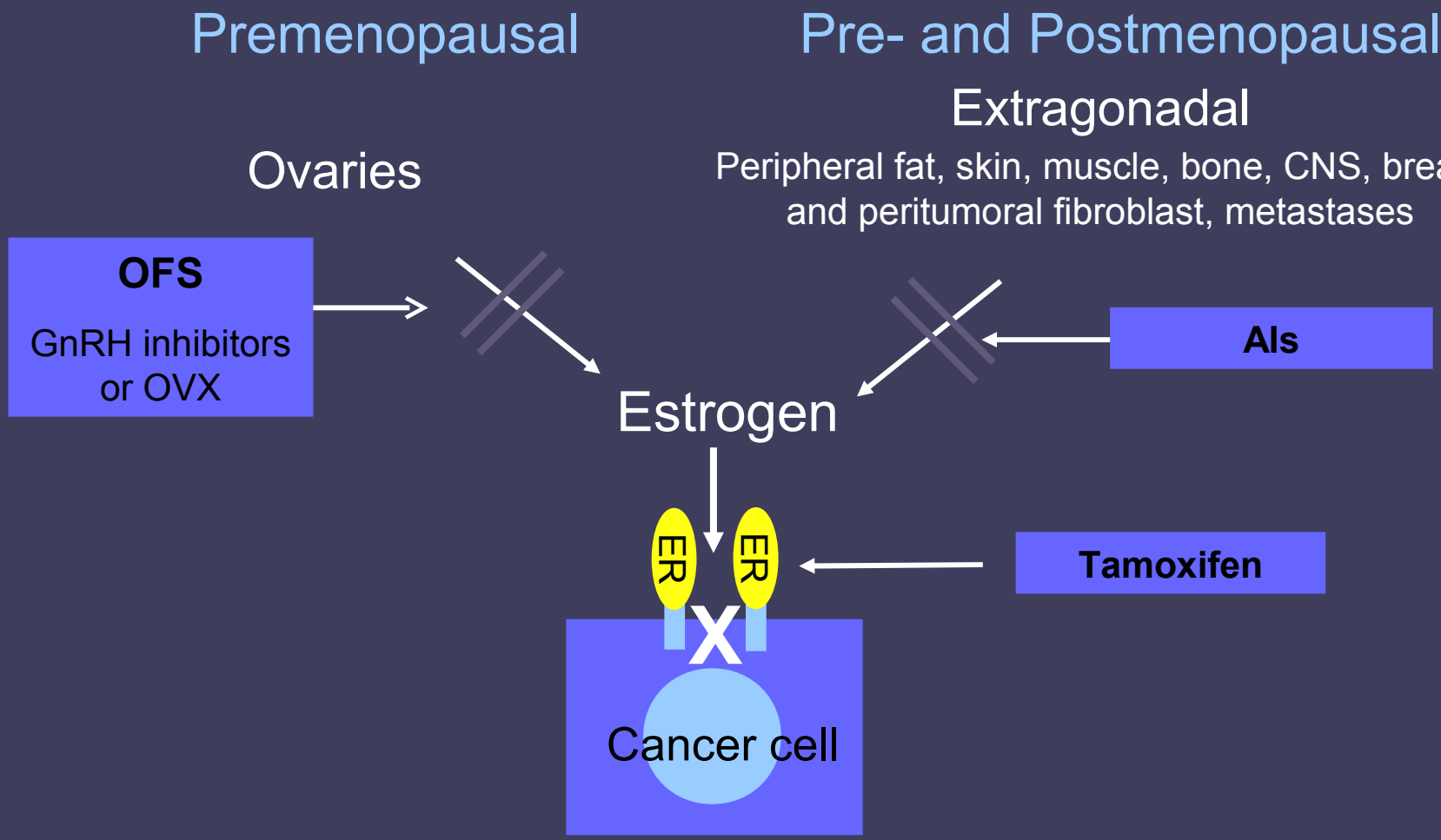
Summary of Adjuvant AI Trial Populations

	ATAC[1]* (n=6241)	BIG 1-98[2] (n=8010)	IES[3] (n=4742)	ABCSG-8/ ARNO 95[4] (n=3224)	ITA[5] (n=448)	MA.17[6] (n=5170)	NSABP B-33[7] (n=1598)
Median age (y)	64.1	61	64.25	62.15	63	62	~60
Node+ (%)	34.2	41.35	44.05	25.5	100	45.65	48
ER+ (%)	83.55†	97.85	81.25	96.5	88.5	97.4†	94
Prior chemo (%)	21.55	25.3	32.25	0	67	45.35	55.5

*No data are included for the combination group; †Only HR+ data are available.
HR+ = hormone receptor–positive.

1. Baum et al. *Lancet*. 2002;359:2131; 2. Thürlimann et al. *N Engl J Med*. 2005;353:2747; 3. Coombes et al. *N Engl J Med*. 2004;350:1081; 4. Jakesz et al. *Lancet*. 2005;366:455; 5. Boccardo et al. *J Clin Oncol*. 2005;23:5138; 6. Goss et al. *J Natl Cancer Inst*. 2005;97:1262; 7. Mamounas et al. *Breast Cancer Res Treat.* 2006;100(suppl 1):S22. Abstract 49.

Antagonizing Estrogen Dependent Growth in Breast Cancer



ATAC: Efficacy Results at 100 Months Median Follow up

- Long-term results showed that anastrozole superior to tamoxifen for DFS, TTR, TTDR, and CLBC, but not for OS and deaths after recurrence
  - Similar findings observed when analyses restricted to hormone receptor–positive population

Outcome (Hormone Receptor–Positive Patients)	**HR (95% CI)**	***P* Value**
DFS	0.85 (0.76-0.94)	0.003
TTR	0.76 (0.67-0.87)	0.0001
TTDR	0.84 (0.72-0.97)	0.022
CLBC	0.60 (0.42-0.85)	0.004
OS	0.97 (0.86-1.11)	0.70
Death after recurrence	0.90 (0.75-1.07)	0.20

Forbes JF, et al. SABCS 2007. Abstract 41.

Patient Characteristics

Characteristic	Switch to Exemestane (n = 2352)	Continue on Tamoxifen (n = 2372)
Demographics		
Median age, years	63	63
Race (%)		
Caucasian	98.4	98.4
Other (including Hispanic, Asian, Black)	1.6	1.6
Adjuvant Chemotherapy (%)		
Yes	32.9	32.4
No	67.1	67.6
Nodal status (%)		
Negative	51.7	51.8
Positive	44.7	44.0
1 to 3 nodes positive	30.7	29.8
4 to 9 nodes positive	10.2	10.3
>9 nodes positive	3.7	3.6
Other*	3.7	4.5

*Includes not reported, unknown, or missing nodal status.

Summary: 52.4-Month Update

- At 25 months after the completion of therapy, switching to Exemestane showed significant improvement in DFS patients treated with 2 to 3 years of tamoxifen
- Switching to Exemestane reduced the risk of dying by 15% for the ITT population (*P*=0.07) and by 17% in ER+/ER unknown early breast cancer (*P*=0.04)
- Exemestane was generally safe and well tolerated after 52.4 months.

Recurrence and Mortality for ATLAS Trial: 10 vs. 5 Years of TAM

Breast Cancer Recurrence

Category	Recurrence Rate/Year		HR
	10-Year Tam	5-Year Tam	
Years 0-1	3.2%	3.6%	0.89 (SE 0.07)
Years 2-4	2.8%	3.3%	0.87 (SE 0.08)
Years 5+	2.4%	3.0%	0.77 (SE 0.12)
Total	2.9%	3.4%	0.866 (SE 0.048)

Breast Cancer Mortality

Category	Death Rate/Year		HR
	10-Year Tam	5-Year Tam	
Years 0-1	1.0%	1.0%	1.00 (SE 0.14)
Years 2-4	1.6%	1.8%	0.90 (SE 0.10)
Years 5+	1.9%	2.4%	0.79 (SE 0.13)
Total	1.4%	1.5%	0.895 (SE 0.070)

Peto et al. Presented at SABCS 2007 (abstract 48)

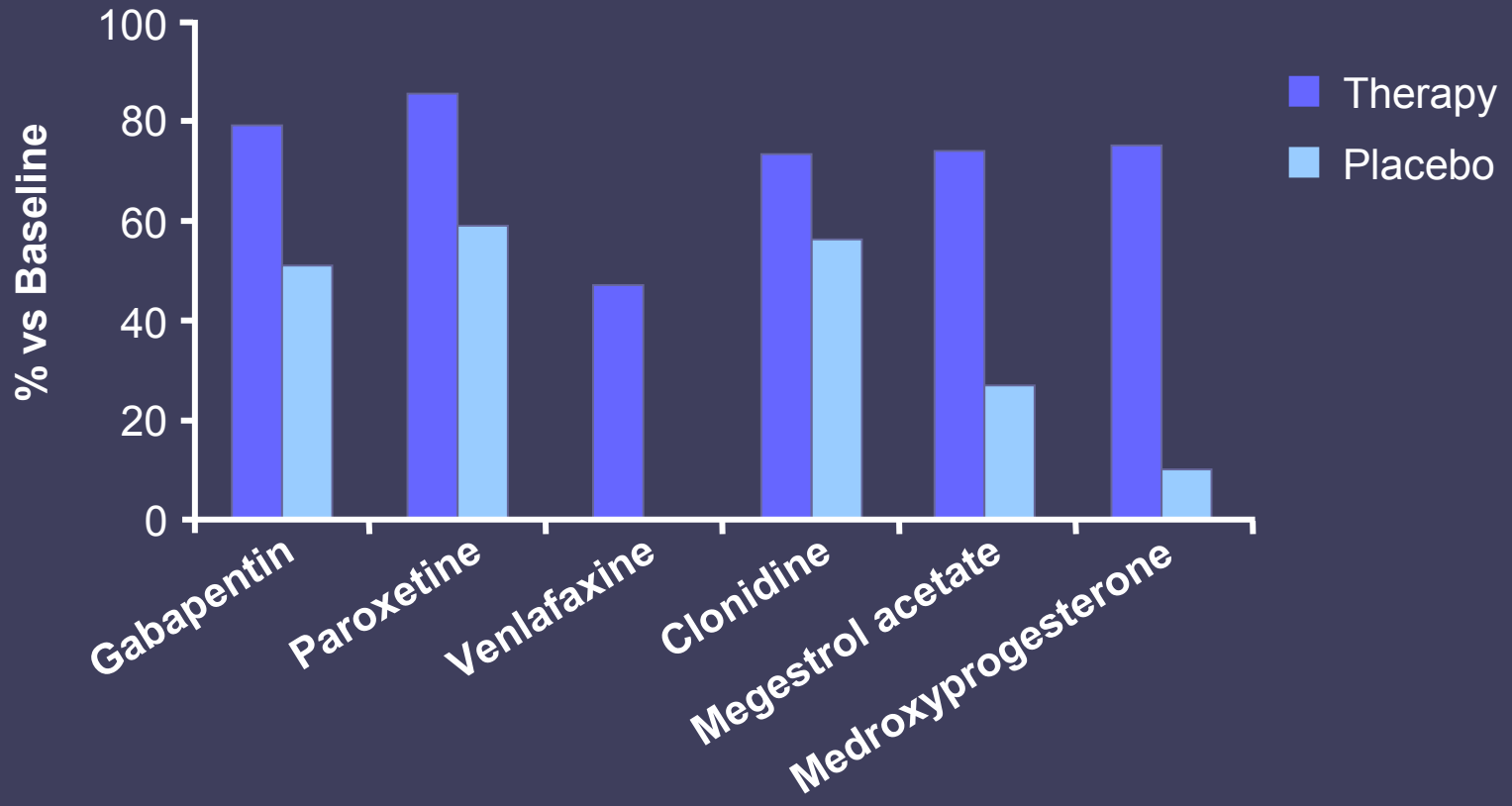
Hot Flashes(潮熱) in Adjuvant AI Trials (cont'd)

Study	Follow-up, months	AI	Reference Drug	AI vs Reference, %	*P* Value
ATAC BIG 1-98	68 26	Anastrozole Letrozole	Tamoxifen Tamoxifen	36 vs 41 34 vs 38 32.8 vs 37.4*	< .0001 < .001
IES ARNO	31 28	Exemestane Anastrozole	Tamoxifen Tamoxifen	42 vs 40 NR	.28
MA-17	30	Letrozole	Placebo	58 vs 54	.003

*51-mo monotherapy analysis.

ATAC Trialists' Group. Lancet. 2005;365:360. Thurlimann B, et al. Eur J. Cancer 2003;39:2310-2317. Thurlimann B, et al. N Engl J Med. 2005;353:2747-2757. Coates AS, et al. ESMO 2006. At: http://www.ibcsg.org/public/documents/pdf/trial_18-98_big1-98/BIG1-98_ESMO_2006.pdf. Coombes RC, et al. J Clin Oncol. 2006;24(18S):933s. Abstract LBA527. Jakesz et al. Breast Cancer Res Treat. 2004;88:57. Abstract 2. Goss PE, et al. J Natl Cancer Inst. 2005;97:1262-1271.

Treatment of Hot Flashes and Night Sweats



Pandya KY, et al. Lancet. 2005;366:818-824. Stearns V, et al. J Clin Oncol. 2005;23:6919-6930. Biglia N, et al. Maturitas 2005;52:78-85. Goldberg RM, et al. J Clin Oncol 2003;25:399-402. Loprinzi CL, et al. N Engl J Med. 1994;331:347-352. Bullock JL, et al. Obstet Gynecol. 1975;46:165-168.

Arthralgia (關節痛)in Adjuvant AI Trials (cont'd)

Study	Follow-up, months	AI	Reference Drug	AI vs Reference, %	*P* Value
ATAC BIG 1-98	68 26	Anastrozole Letrozole	Tamoxifen Tamoxifen	36 vs 29 20 vs 12 20.0 vs 13.5*	< .0001 < .001
IES ARNO	55 28	Exemestane Anastrozole	Tamoxifen Tamoxifen	21 vs 15 NR	< .001
MA-17	30	Letrozole	Placebo	25 vs 21	< .001

*51-mo monotherapy analysis.

ATAC Trialists' Group. Lancet. 2005;365:360. Thurlimann B, et al. Eur J. Cancer 2003;39:2310-2317. Thurlimann B, et al. N Engl J Med. 2005;353:2747-2757. Coates AS, et al. ESMO 2006. At: http://www.ibcsg.org/public/documents/pdf/trial_18-98_big1-98/BIG1-98_ESMO_2006.pdf. Coombes RC, et al. J Clin Oncol. 2006;24(18S):933s. Abstract LBA527. Jakesz et al. Breast Cancer Res Treat. 2004;88:57. Abstract 2. Goss PE, et al. J Natl Cancer Inst. 2005;97:1262-1271.

Cognitive Effects AIs vs Tamoxifen

Postmenopausal Women

Tamoxifen

AI

Cognitive Function in AI Trials

- Exemestane: TEAM Trial
  - Similar rates of cognitive problems and anxiety, depression, fatigue, and menopausal complaints in tamoxifen and exemestane users
  - Tamoxifen users score significantly lower on a “mental flexibility” test ($P = .007$) and a category fluency” test ($P < .0001$) than healthy controls
  - Tamoxifen < exemestane users on attention, letter fluency, verbal memory, and visual association tests
- Anastrozole
  - Pilot study in early breast cancer: anastrozole (n = 15) vs tamoxifen (n = 16)
  - Patients receiving anastrozole experienced more severe impairment in cognitive function than those receiving tamoxifen

Bender CM, et al. SABCS 2005. Abstract 6074.
Schilder C, et al. ASCO 2007. Abstract 566.

Cardiovascular Events（心血管病）in Adjuvant AI Trials

No significant increases in cardiovascular events with AI compared with tamoxifen or placebo

- Ischemic cardiac or cardiovascular events
  - ATAC: anastrozole 4.1% vs tamoxifen 3.4% (*P* = .10)
  - BIG 1-98: letrozole 4.1% vs tamoxifen 3.8% (*P* = .61)
  - IES: exemestane 9.9% vs tamoxifen 8.6% (*P* = .12)
  - MA.17: letrozole 5.8% vs placebo 5.6% (*P* = .76)
- Similar rates also for myocardial infarctions and cerebrovascular accidents or transient ischemic attacks

Arimidex [package insert]. 2005. Thurlimann B, et al. N Engl J Med. 2005;353:2747-2757. Dunn C and Keam SJ. Pharmacogenomics. 2006;24:495-517. Coombes RC, et al. J Clin Oncol. 2006;24(18S):933s. Abstract LBA527. Goss PE, et al. J Natl Cancer Inst. 2005;97:1262-1271.

Cardiovascular Events（心血管病）in Adjuvant AI Trials

	Letrozole[1,2,3]	Anastrozole[4]	Exemestane[5]
Relative increase (vs tamoxifen)	NS	NS	NS
Absolute increase (vs tamoxifen)	0.3% to 0.5%	0.7%	1.3%
Relative increase (vs placebo)	0	NR	?

1. Thurlimann B, et al. N Engl J Med. 2005;353:2747-2757. 2. Coates AS, et al. J Clin Oncol. 2007;25:486-492. 3. Goss PE, et al. J Natl Cancer Inst. 2005;97:1262-1271. 4. Howell A, et al. Lancet. 2005;365:60-62. 5. Coombes et al. J Clin Oncol. 2006;24(18S):933a. Abstract LBA527.

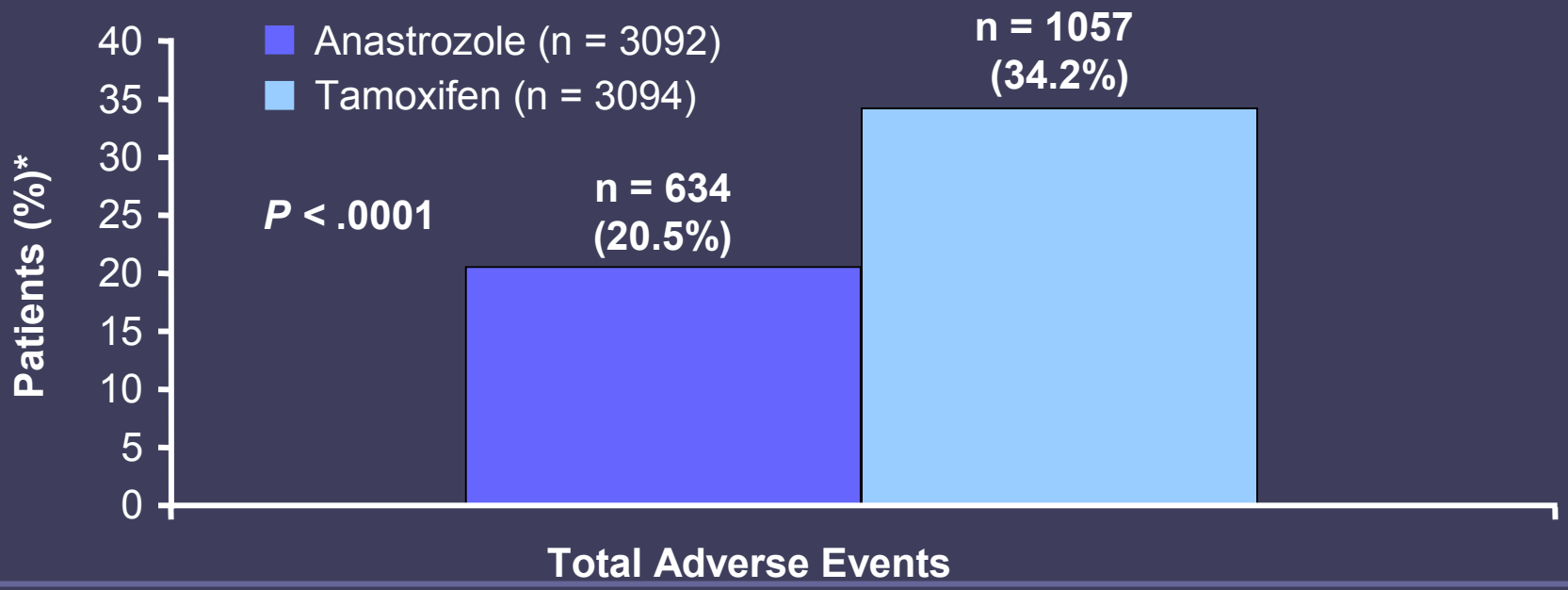
ATAC Endometrial Subprotocol (婦科病徵)(2 Years)

	Anastrozole (N = 70)	Tamoxifen (N = 53)	Baseline (N = 254)
Total abnormal, n (%)	6 (9)	9 (17)	45 (18)
▪ Polyp (no atypia), n	5	8	20
▪ Polyp (atypia unknown), n	1	0	0
• Secretory/proliferative endometrium, n	1	0	23
▪ Atypical hyperplasia, n	0	1	1
▪ Complex hyperplasia, n	0	0	0
▪ Other, n	0	0	1
Total normal, n (%)	64 (91)	44 (81)	209 (82)

Serious abnormality = 1 patient with atypical hyperplasia and 1 patient with “other” abnormality

ATAC Trialists’ Group. Lancet. 2005;365:60-62.

ATAC Total Gynecologic Adverse Events（婦科病徴）

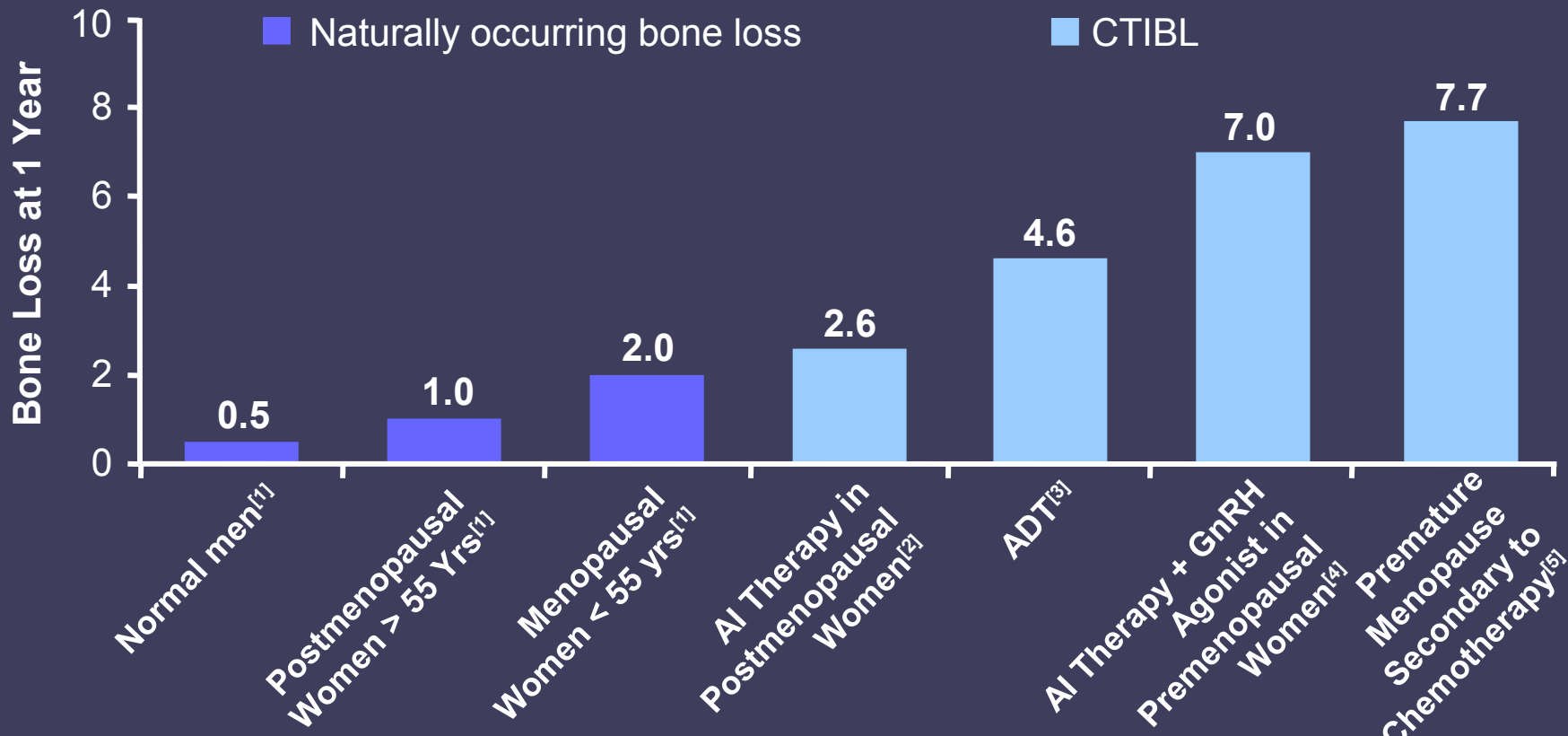


Major differences (> 3%) between the anastrozole and tamoxifen groups in the number of patients experiencing a particular category of adverse event were noted for 4 categories: vaginal hemorrhage, leukorrhea, endometrial hyperplasia, and endometrial neoplasia

*All patients who received trial treatment.

Duffy S, et al. BJOG. 2003;110:1099-1106.

Bone Loss With Cancer Therapies（骨骼健康）



1. Kanis JA. Osteoporosis.1997:22-55. 2. Eastell R, et al. J Bone Mineral Res. 2002. 3. Maillefert JF, et al. J Urol. 1999;161:1219-1222. 4. Gnant M. SABCS 2002. Abstract. 5. Shapiro CL, et al. J Clin Oncol. 2001;19:3306-3311.

Indirect Fracture Rate Comparisons（骨骼健康）

Clinical Study	Setting/Mean Age, Yrs	Fracture Rate/1000 Patients per Yr
ATAC (N = 6185)	Early breast cancer (adjuvant)/64	Anastrozole: 21.55 Tamoxifen: 13.44
BIG 1-98 (N = 7945)	Early breast cancer (adjuvant)/64	Letrozole: 22.0 Tamoxifen: 15.0
IES (N = 4724)	Early breast cancer (adjuvant)/64	Exemestane: 20.1 Tamoxifen: 16.0
WHI (N = 16,608)	Healthy women/63 (50-69 yrs: 45%)	HRT (total): 14.75 Placebo (total): 19.10

Do the Steroidal and Nonsteroidal AIs Differ in Their Effects on Bone?

PRO

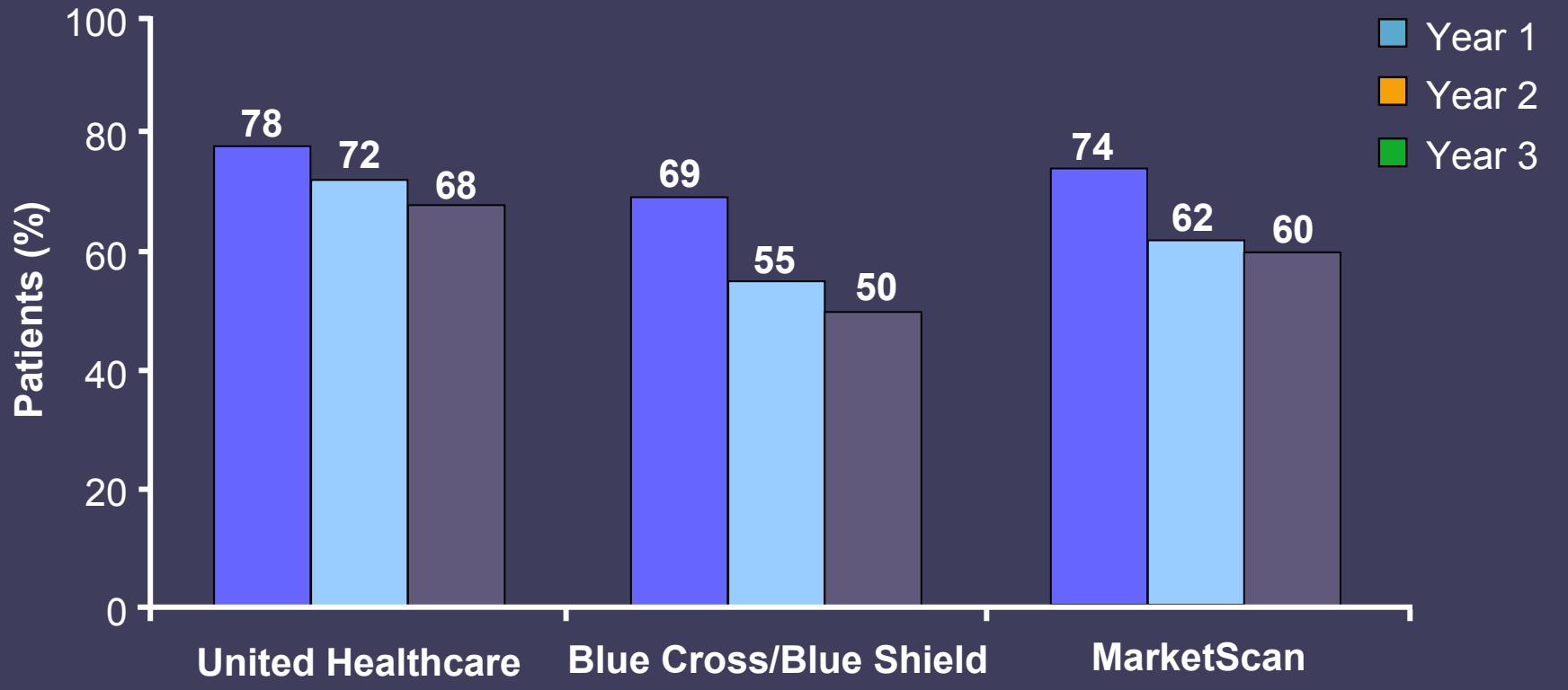
- Exemestane weakly androgenic
- Animal data show androgenic effect of exemestane but not letrozole on bone
- BMD changes in IES appear less after 1st year than in ATAC/MA-17
- BMD changes with exemestane vs placebo similar- at 24 mo BMD at LS –1.47 and Fem Neck – 1.92. At 36 mo LS = placebo and Fem Neck recovering (-1.55% vs plac)[1]

CON

- Similar increase in fracture incidence in phase III trials
- 2 studies of AIs in healthy volunteers: one study increased P1NP bone formation marker suggestive of androgenicity with exemestane[2] and not the nonsteroidals; other study (LEAP) does not [3]

1. Lonning PE, et al JCO 2005;23:5126-5137. 2. Goss P, et al. Breast Cancer Res Treat. 2002;76(suppl 1):S107. Abstract 415. 3. McCloskey E, et al ASCO 2006. Abstract 555.

Poor Adherence of AI Therapy After 36 Months



Consistent yearly decrease of adherence
The most symptomatic patients may be those who could benefit most

Partridge AH, et al. SABCS 2006. Abstract. 4044.

Summary of Effects of AIs on Symptoms and End Organs

- The profound estrogen suppression by AIs causes “minimenopause” symptoms including hot flashes, myalgia, arthralgia, and urogenital symptoms
- AI symptoms differ from tamoxifen—the impact from either on quality of life is low—particularly when AI given after tamoxifen
- AIs have a beneficial effect on the endometrium and no adverse effect on thromboembolism
- AIs have no impact on lipid metabolism
- When compared with tamoxifen, AIs are associated with a slightly higher incidence of cardiovascular effects that likely represents cardioprotection by tamoxifen

Summary of Effects of AIs on Symptoms and End Organs (cont'd)

- Estrogen suppression by AIs mildly increases bone resorption that is easily overcome by bisphosphonates and reverses within 12-24 months after therapy is discontinued
- The steroidal AI exemestane and its principal metabolite 17OH exemestane differ from the nonsteroidals and have mild androgenic effects
  - The MA.27 clinical trial will answer whether these effects cause differences in efficacy or toxicity
- Compliance to AIs in clinical practice is poor—this may be due to pharmacodynamically determined toxicity
  - Under investigation in the MA.27 trial