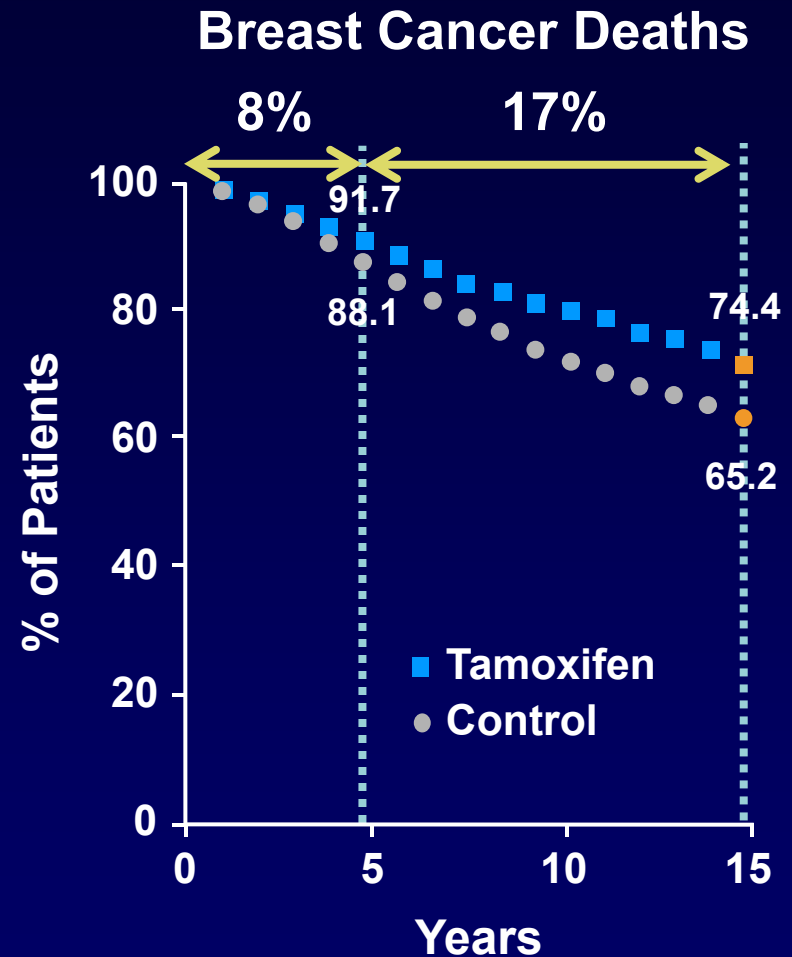
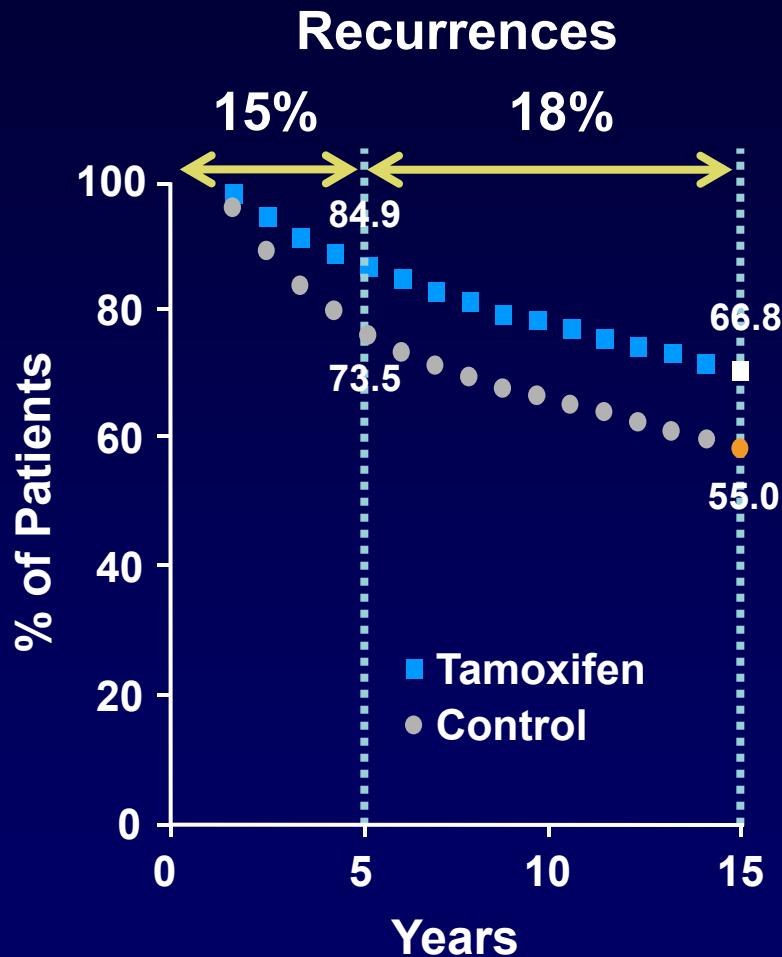


**Managing Endocrine-Responsive
Breast Cancer:
Have All The Necessary Questions
Been Asked to Guide Us Forward?**

Henning T. Mouridsen, MD, PhD
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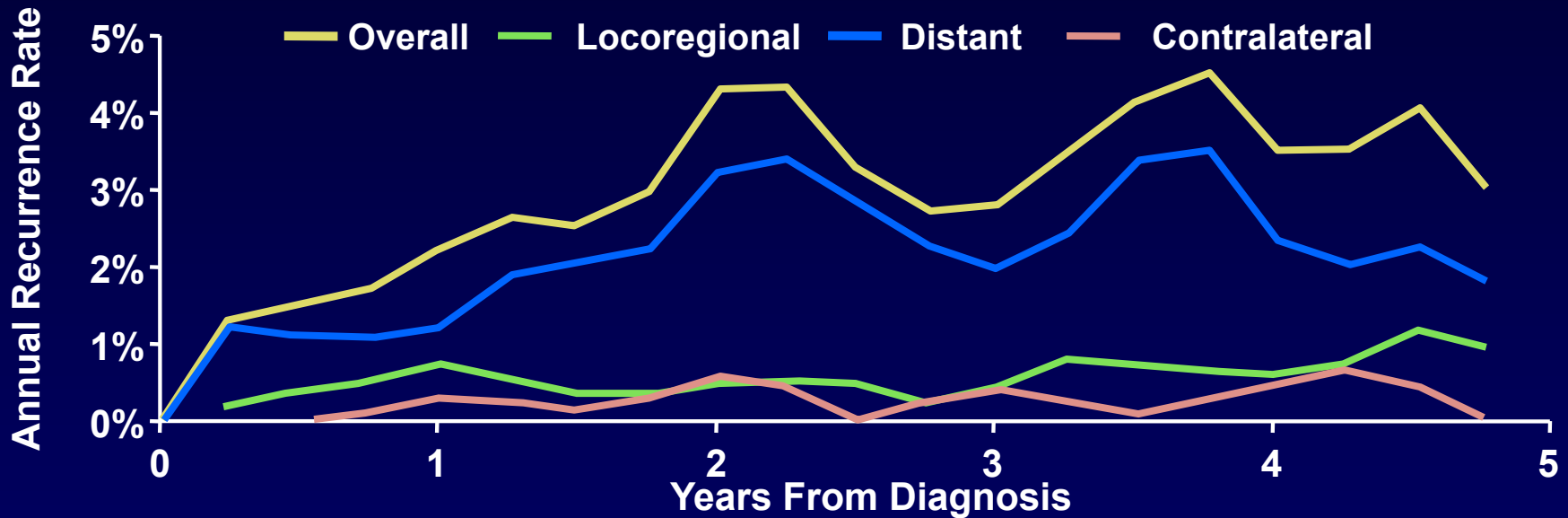
Recurrences and Deaths Continue to Occur With Tamoxifen



Adapted from Early Breast Cancer Trialists' Collaborative Group Meeting, 2000.
Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 2005;365(9472):1687-1717.

Early Peak of Recurrences and Distant Metastases Despite Tamoxifen Treatment

- 3614 postmenopausal women with ER+ operable breast cancer, all treated with tamoxifen



	Cumulative Recurrence Rates, %	
	2.5 Years	5 Years
Overall	6.3	13.9
Distant	4.8	10.5
Locoregional	1.1	3.0
Contralateral	0.5	1.2

ER+, estrogen receptor-positive

Mansell J, et al. *Breast Cancer Res Treat.* 2009;117(1):91-98.

Development of Aromatase Inhibitors

- **Three highly potent and specific aromatase inhibitors (AIs) are approved for treatment of ER+ breast cancer**
 - Nonsteroidal inhibitors (anastrozole, letrozole)
 - Steroidal inactivator (exemestane)
- **Are all AIs the same?**
 - In potency?
 - In efficacy?
 - In toxicity?

Effect of AIs on Aromatization and Plasma Estrogen in Postmenopausal Women

AI	Aromatase Activity	% Suppression		
		Estradiol	Estrone	Estrone Sulfate
Aminoglutethimide ¹	90.6	75.7	NR	NR
Anastrozole 1 mg ²	96.7 <i>P</i> = .003	92.8 <i>P</i> = .018	96.3 <i>P</i> = .003	95.3 <i>P</i> = .003
Letrozole 2.5 mg ³	>99.1	95.2	98.8	98.9
Exemestane 25 mg ⁴	97.9	92.2	94.5	93.2

NR, not reported

1. MacNeill FA, et al. *Br J Cancer* 1992;66(4):692-697. 2. Geisler J, et al. *Br J Cancer*. 1996;74(8):1286-1291.
3. Geisler J, et al. *J Clin Oncol*. 2002;20(3):751-757. 4. Geisler J, et al. *Clin Cancer Res*. 1998;4:2089-2093.

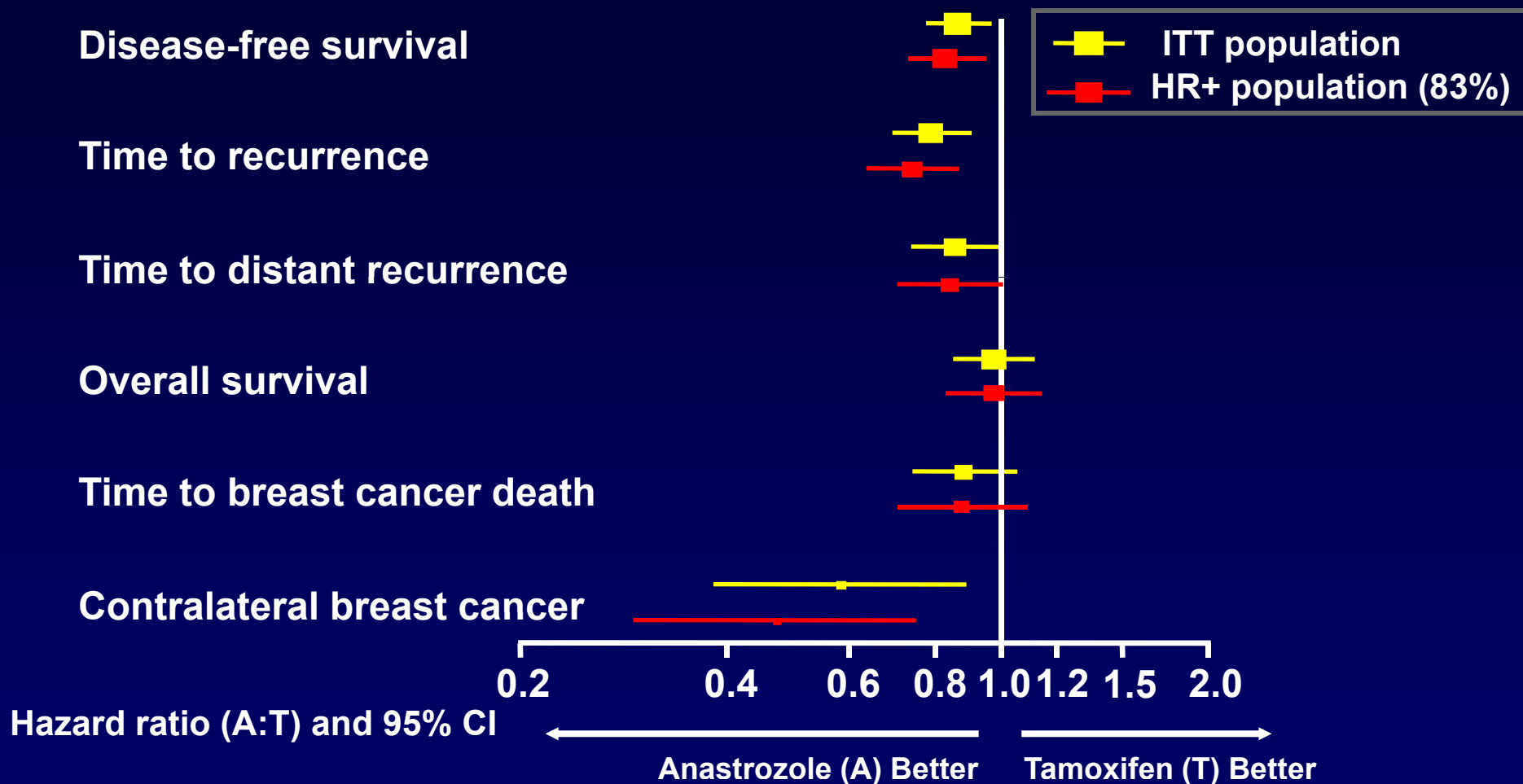
Do differences in potency translate into differences in efficacy in the adjuvant setting in terms of

- Reduction in risk of early distant metastases**
- Reduction in mortality**

Upfront Trials of 5 Years Tamoxifen vs Aromatase Inhibitor

Study	AI
ATAC	Anastrozole
BIG 1-98	Letrozole

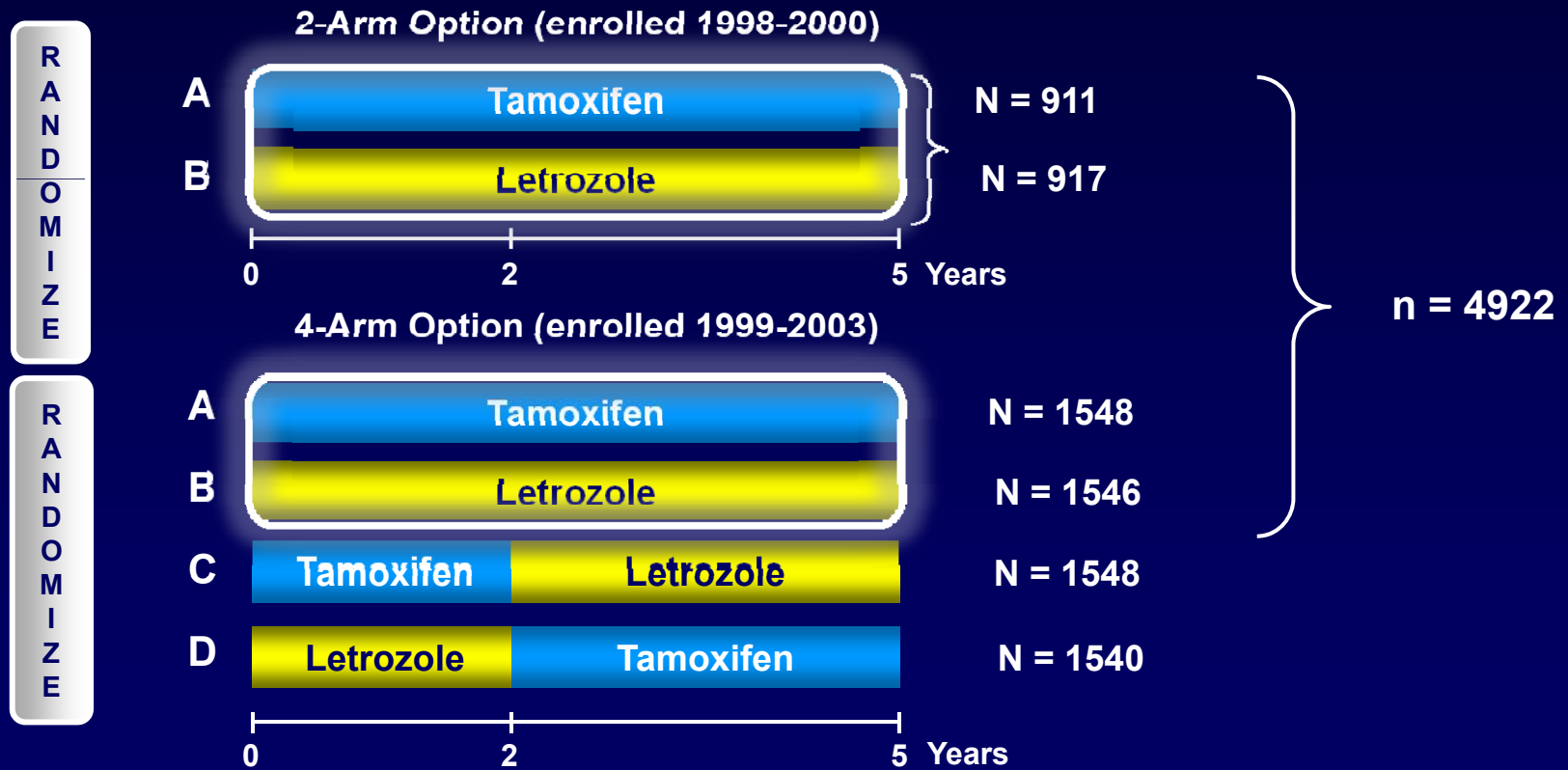
ATAC 68 Months Efficacy Analysis



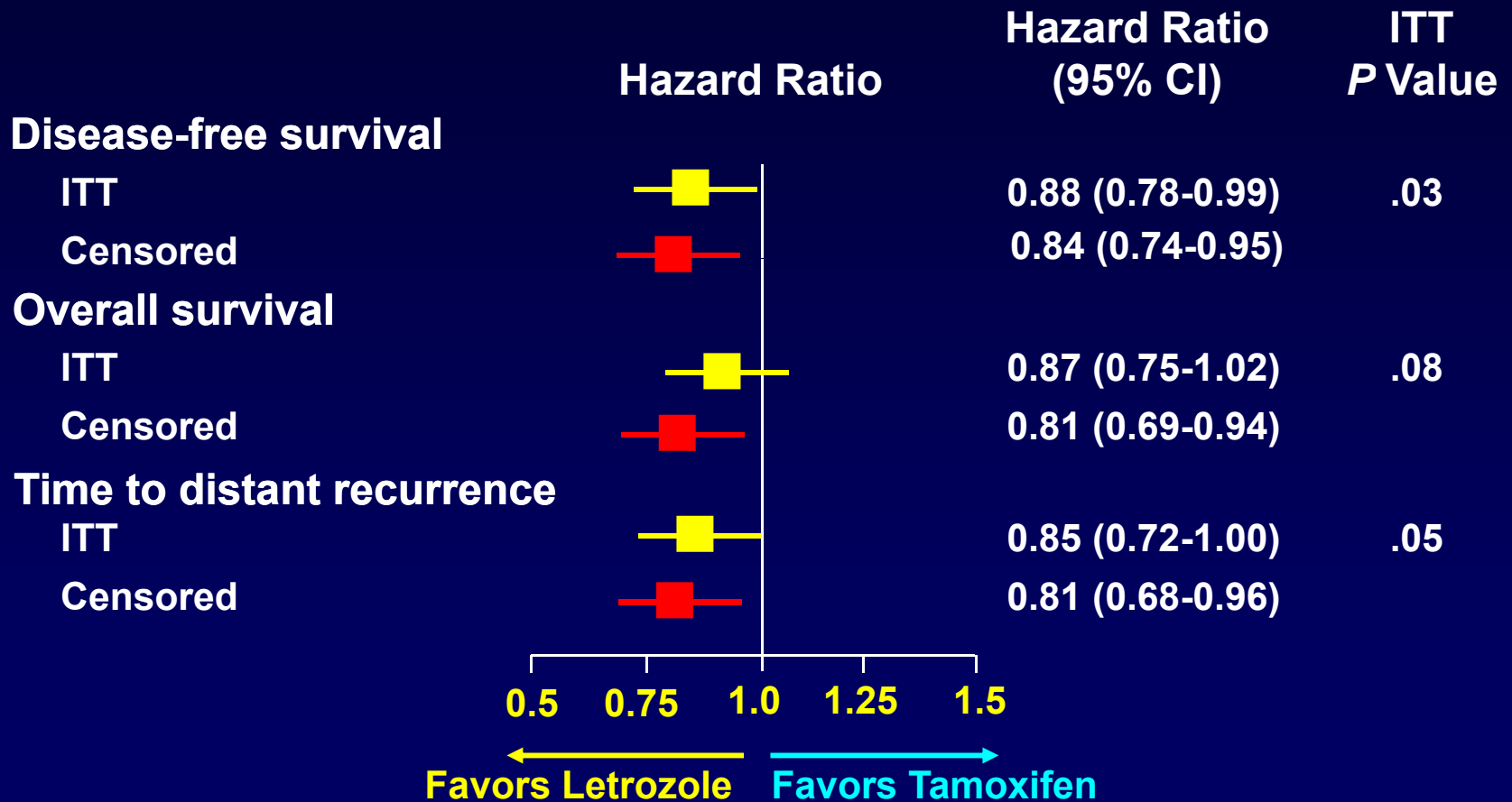
HR+, hormone receptor-positive; ITT = intent-to-treat

Howell A, et al. *Lancet*. 2005;365(9453):60-62. Howell A. *Breast Cancer Res Treat*. 2004;88(Suppl 1): Abstract 1.

BIG 1-98 Monotherapy Comparison: Tamoxifen vs Letrozole



BIG 1-98 Monotherapy Update Median Follow-Up 76 Months



BIG 1-98: Inverse Probability of Censor Weighting (IPCW)

- The purpose of the IPCW is to adjust intent-to-treat (ITT) analyses for potential bias caused by non-adherence with the randomized trial design and thus used to estimate the true treatment
- The goal of this analysis is to evaluate the magnitude the benefits of LET vs TAM for 5 years, as it would have been had patients randomized to TAM not selectively crossed over to LET

BIG 1-98: Results from the 10-Year Follow-Up

- The selective crossover affects the efficacy results of the ITT analysis monotherapy comparison
- Additional IPCW analysis accounting for the selective crossover indicates that the benefit of LET over TAM is greater than in the ITT analysis. LET for 5 years is significantly better than TAM for DFS and OS

Analysis (mo/yr presented)	HR [LET vs TAM 5 Year] (95% CI)	
	DFS	OS
ITT (76 mo)	0.88 (0.78-0.99)	0.87 (0.75-1.02)
Censor TAM pts at selective crossover to LET (76 mo)	0.84 (0.74-0.95)	0.81 (0.69-0.94)
IPCW (76 mo)	0.85 (0.76-0.96)	0.83 (0.71-0.97)

Does Higher AI Potency Translate to Better Efficacy in the Adjuvant Setting

Indirect Evidence From Upfront Trials of AIs vs TAM

Endpoint	Letrozole	Anastrozole
 Early DM	Yes ¹⁻³	No ⁴⁻⁵
OS	Strong trend ⁶	No ⁷

DM, distant metastasis; OS, overall survival; RR, response rate; TTP, time to progression

Reviewed by Mouridsen H. 2009:

1. Thürlimann B, et al. *N Engl J Med.* 2005;353(26):2747-2757. 2. Coates AS, et al. *J Clin Oncol.* 2007;25(5):486-492. 3. Mauriac L, et al. *Ann Oncol.* 2007;18(5):859-867. 4. Howell A, et al. *Lancet.* 2005;365(9453):60-62. 5. Howell A, et al. Presented at: 11th International St Gallen Primary Therapy of Early Breast Cancer Conference; March 11-14, 2009: St Gallen, Switzerland. Abstract 0130. 6. Mouridsen H, et al. *N Engl J Med.* 2009;361(8):766-776. 7. Forbes JF, et al. *Lancet Oncol.* 2008;9(1):45-53.

Adverse Events in Adjuvant Trials of LET or ANA vs TAM and LET vs Placebo

	Upfront LET or ANA vs TAM ¹	LET vs Placebo ²
Hot flushes	↓	↑
Arthralgia	↑	↑
Thromboembolic disorder	↓	↑
Osteoporosis/fractures	↑	↑
Gynecologic symptoms	↓	↓
Hypercholesterolemia	↑	—
Cardiovascular events	↑	—

Similar adverse events observed with LET vs TAM and ANA vs TAM

ANA, anastrozole; LET, letrozole; TAM, tamoxifen

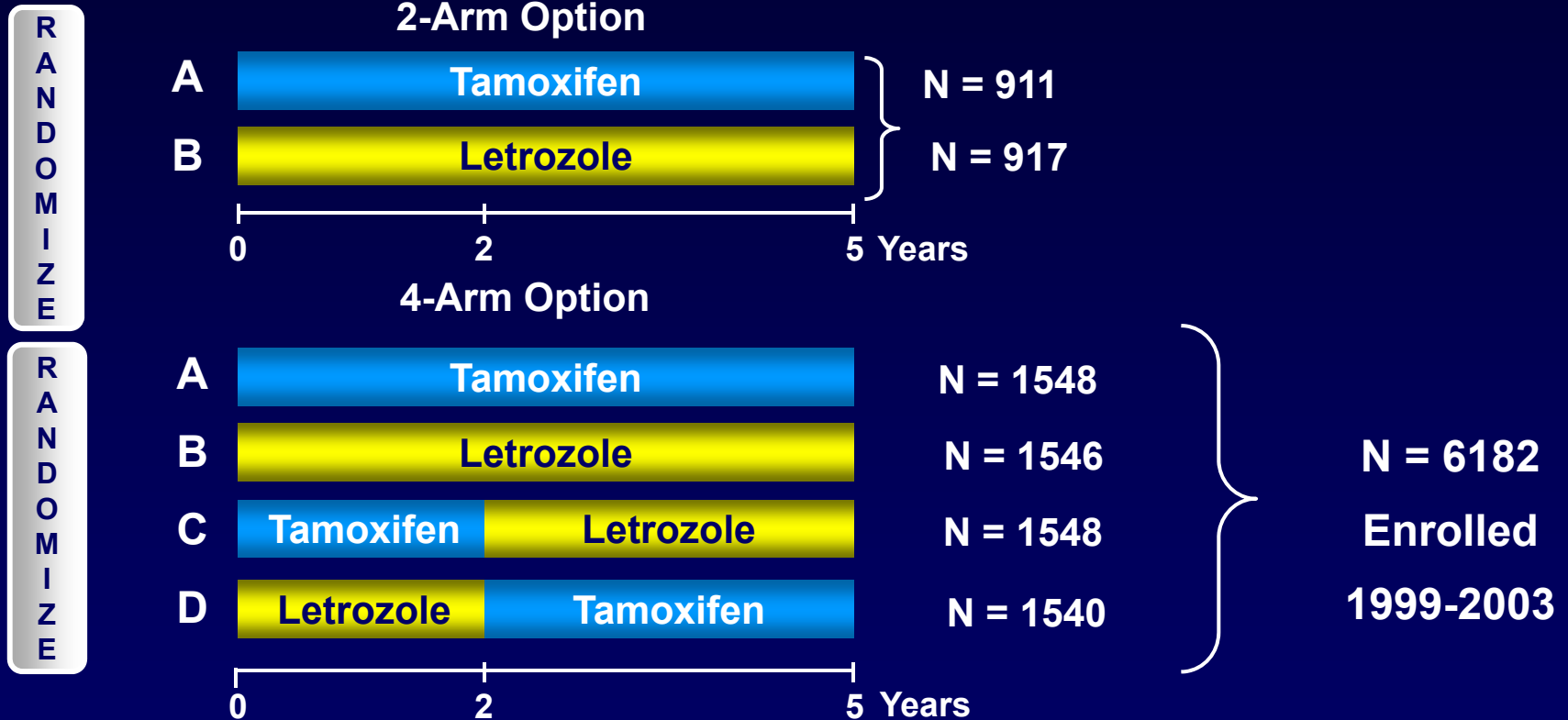
1. Mouridsen H. *Curr Med Res Opin.* 2006;22(8):1609-1621. 2. Goss PE, et al. *J Clin Oncol.* 2008;26:1948-1955.

3. Thürlimann B, et al. Presented at: 11th International St Gallen Primary Therapy of Early Breast Cancer Conference; March 11-14, 2009: St Gallen, Switzerland. Abstract 0161.

Upfront Trials of 5 Years of AI vs the Sequence of AI/TAM

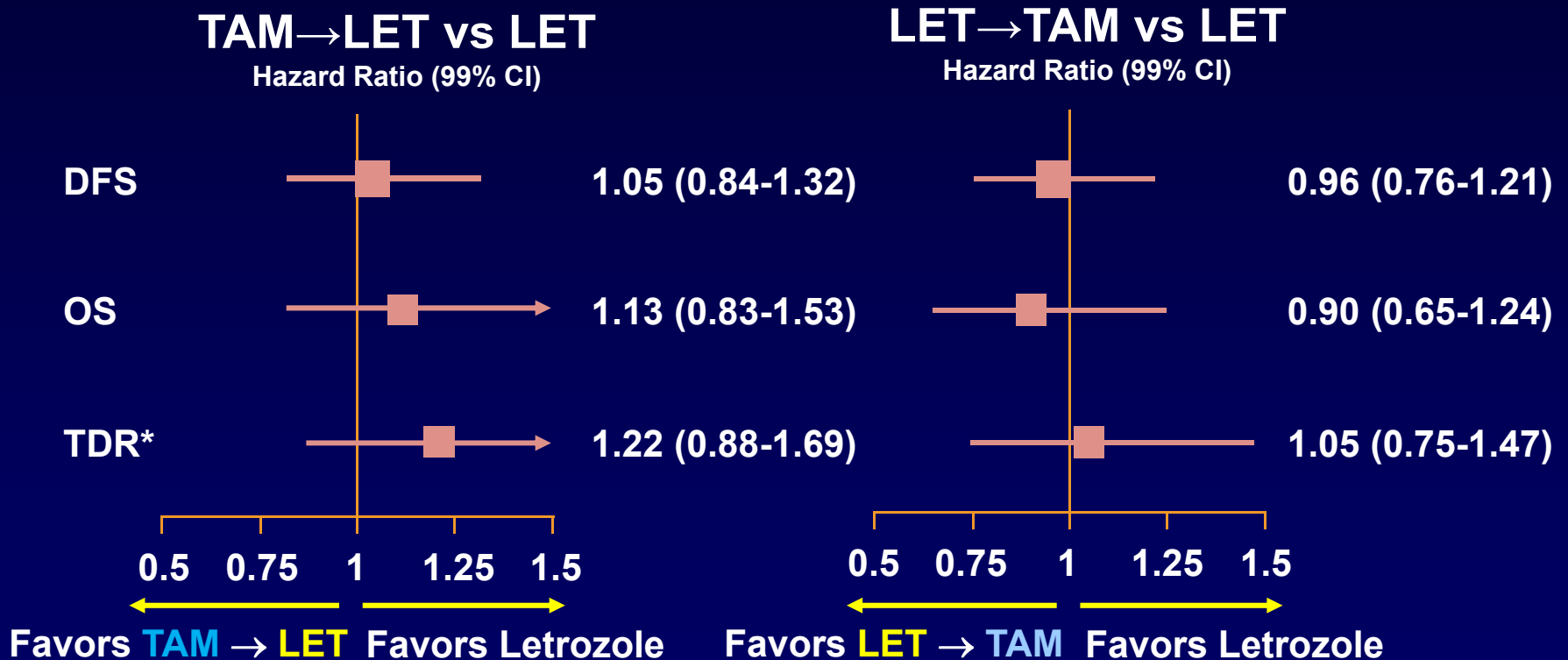
Study	AI	Sequence
BIG 1-98	LET	TAM → LET
		LET → TAM
TEAM	EXE	TAM → EXE

BIG 1-98 Sequential Therapy



*612 patients (39.5%) received letrozole after the tamoxifen arm was unblinded. The present analysis includes only 3 blinded arms (B, C, D).

Sequential Treatment Comparisons Median Follow-up 71 Months



*Time to distance recurrence

Mouridsen H, et al. *N Engl J Med.* 2009;361(8):766-776.

Duration of Upfront Letrozole

- Prolonged follow-up is required to know if 2 years LET followed by switch to TAM is safe
- Temporary carry-over effect
- Potential bias from extended letrozole after study drug discontinuation

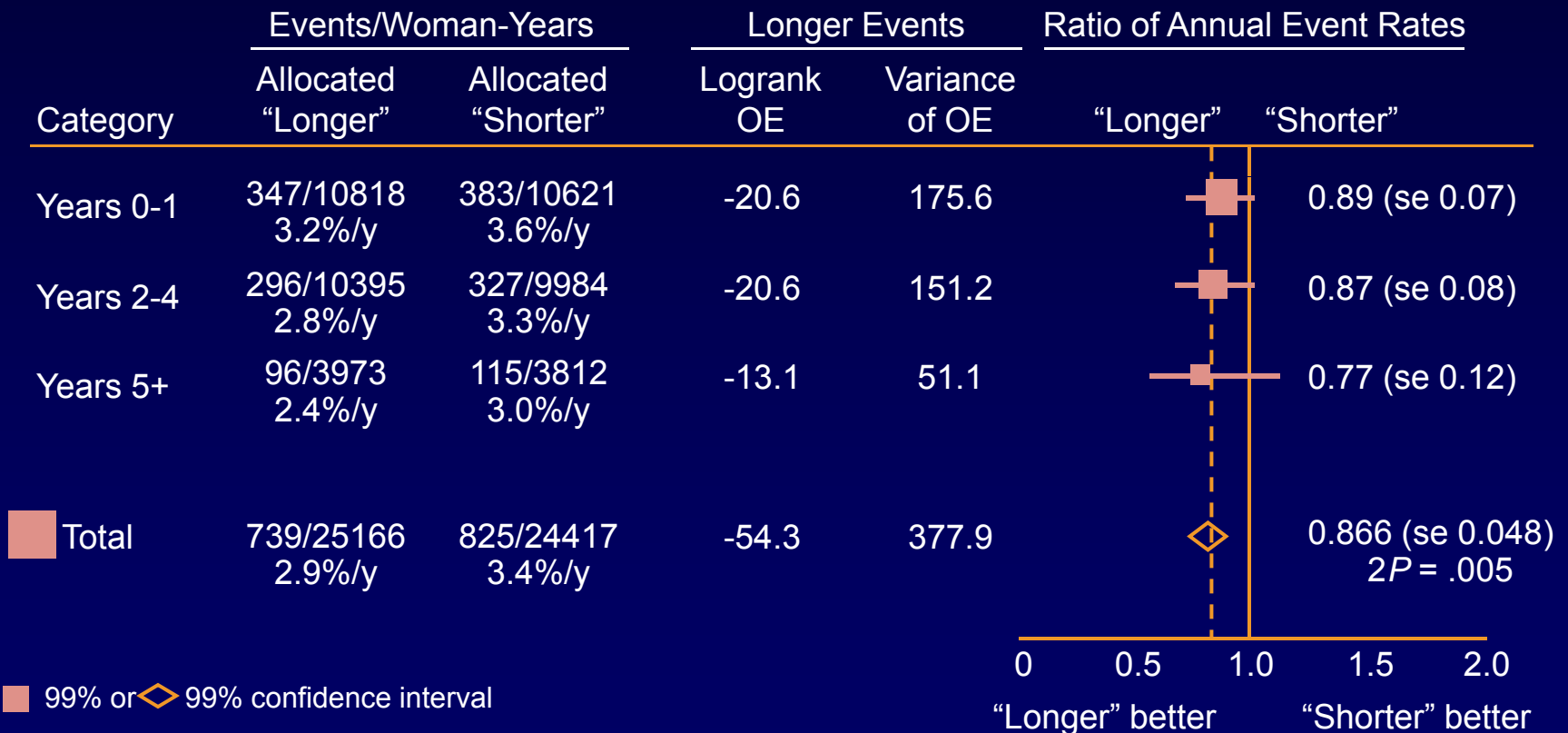
Duration of Endocrine Therapy

We know

- **That ER-positive breast cancer is a chronic disease**
- **That extended therapy with AI and TAM is beneficial**

ATLAS (N = 11,500): 10 vs 5 Years Tamoxifen, ER+/?

Recurrence



Heterogeneity between 3 categories: $X_2^2 = 0.8$; $P > .1$; NS

Treatment effect $2P = .505$

Test for trend: $X^2 = 0.6$; $2P > .1$; NS

Improved Outcome with Extended Adjuvant AI Therapy After 5 Years of Tamoxifen

MA.17¹⁻³

- Extended adjuvant LET after TAM significantly improved DFS and DDFS in both node-positive and node-negative patients and OS for node-positive patients
- Longer duration of LET is associated with significantly greater benefit
- A post-unblinding analysis demonstrated that those patients who started LET after a prolonged period off TAM (1-7 years) still benefited from the drug

ABCSG-6a⁴

- Significantly reduced risk of recurrence with ANA

NSABP B-33⁵

- Premature closure; some on placebo switched to EXE (or LET)
- Nevertheless, in ITT analysis by initial intention, EXE improved 4-year DFS and RFS

RFS, relapse-free survival

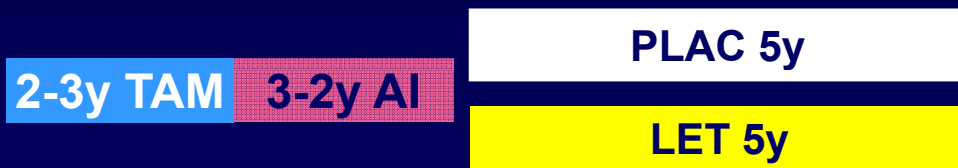
1. Goss PE, et al. *J Natl Cancer Inst.* 2005;97(17):1262-1271. 2. Ingle JN, et al. *Breast Cancer Res Treat.* 2006;99(3):295-300. 3. Goss PE, et al. *J Clin Oncol.* 2008;26(12):1948-1955. 4. Jakesz R, et al. *J Natl Cancer Inst.* 2007;99(24):1845-1853. 5. Mamounas EP, et al. *J Clin Oncol.* 2008;26(12):1965-1971.

Extending Duration of Adjuvant AI Therapy

NCIC CTG - MA.17R (10 Years vs 5 Years)



NSABP B-42

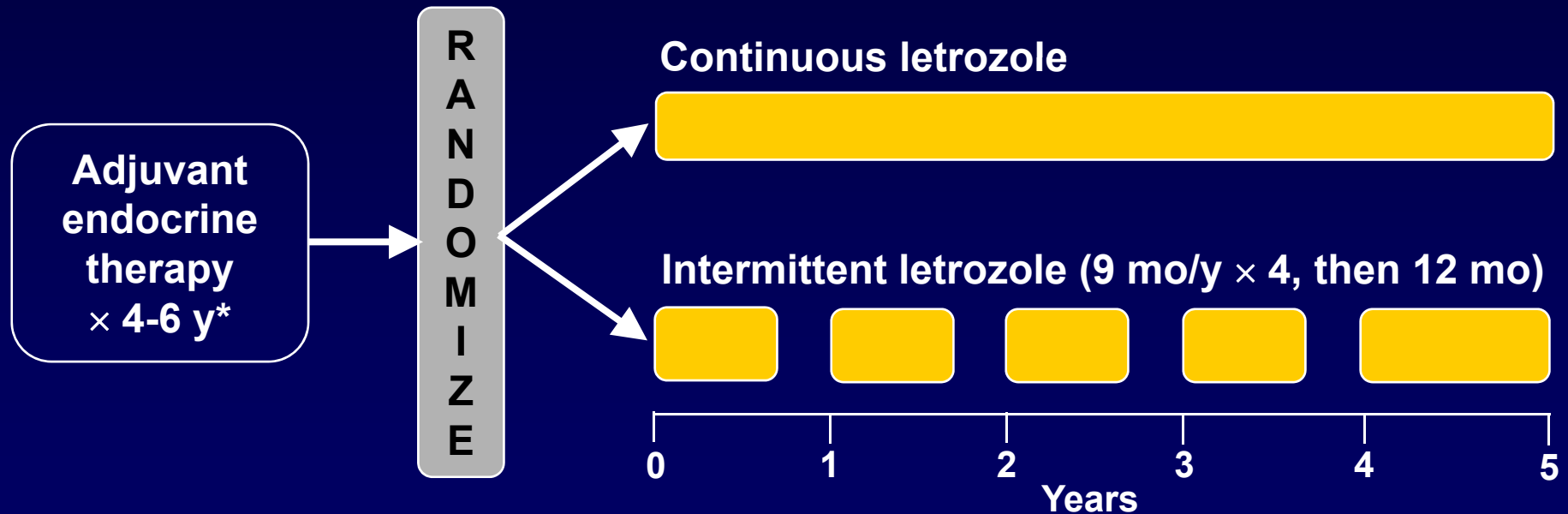


SALSA (ABCSG 16)



Study of Letrozole Extension (SOLE)

- Phase III trial—HR+ node+ breast cancer
- Hypothesis: Periodic 3-month treatment-free intervals will improve DFS



- Activated 2007
- Target accrual: 4800

* Disease-free and postmenopausal when randomized

Summary

- **Upfront therapy with aromatase inhibitors**
 - Results in improved DFS and improved time to distant recurrence
 - Improved reduction in early distant metastases and strong trend toward improved overall survival with letrozole (BIG 1-98)
- **Sequential therapy**
 - Data from BIG 1-98 confirm that treatment should start with an AI (letrozole), and whether switching to tamoxifen after 2+ years of letrozole is as efficient as continuing on letrozole for 5 years remains to be evaluated
- **Duration of therapy**
 - Hormone receptor–positive breast cancer is a chronic disease and extending therapy with an AI after 5 years tamoxifen reduces recurrence

Unanswered Questions

- **What is the best AI therapy?**
 - FACE trial (letrozole vs anastrozole)
 - MA.27 trial (exemestane vs anastrozole)
- **What is the optimal duration of therapy with AIs?**
 - NCIC CTG – MA.17R (10 years vs 5 years)
 - NSABP B-42
 - SALSA (ABCSG 16)
- **Mode of administration of extended AI**
 - SOLE
- **Is there a role for tamoxifen following AIs?**
- **Is there a role for genomics in selection of appropriate hormone therapy?**
 - Should any patients receive tamoxifen upfront?
 - Who is at the highest risk of late relapse?
 - What factors define resistance to hormone therapy?