

# Case #4—Perimenopausal Breast Cancer: What Is the Optimal Therapy?

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# Our Patient

## What is good?

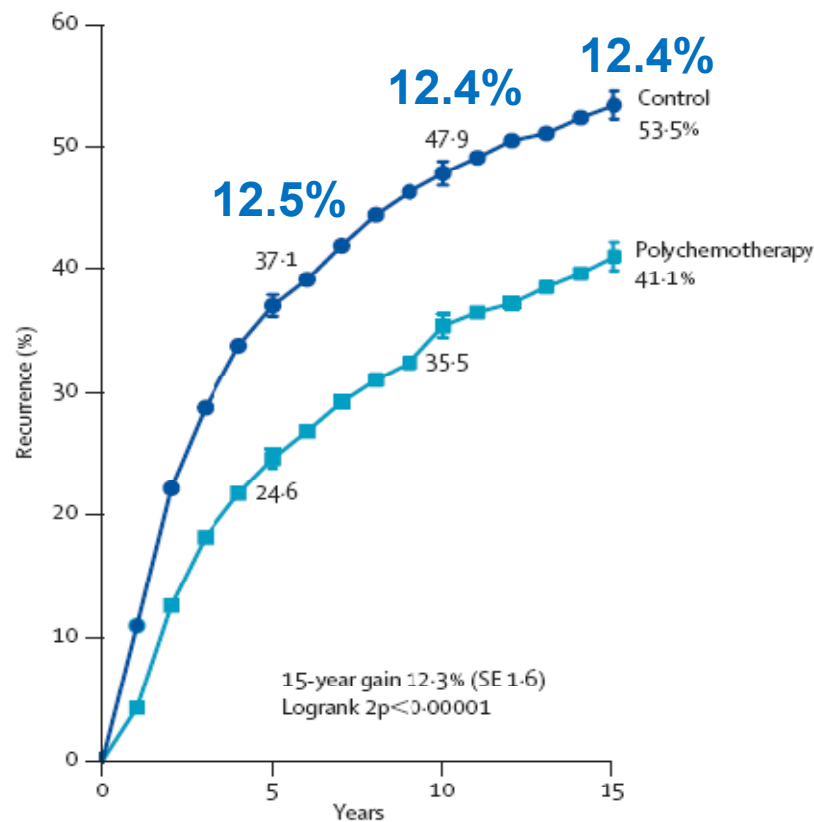
- Postmenopausal?
- No adverse histology
- ER/PR +
- ECOG 0

## What is bad?

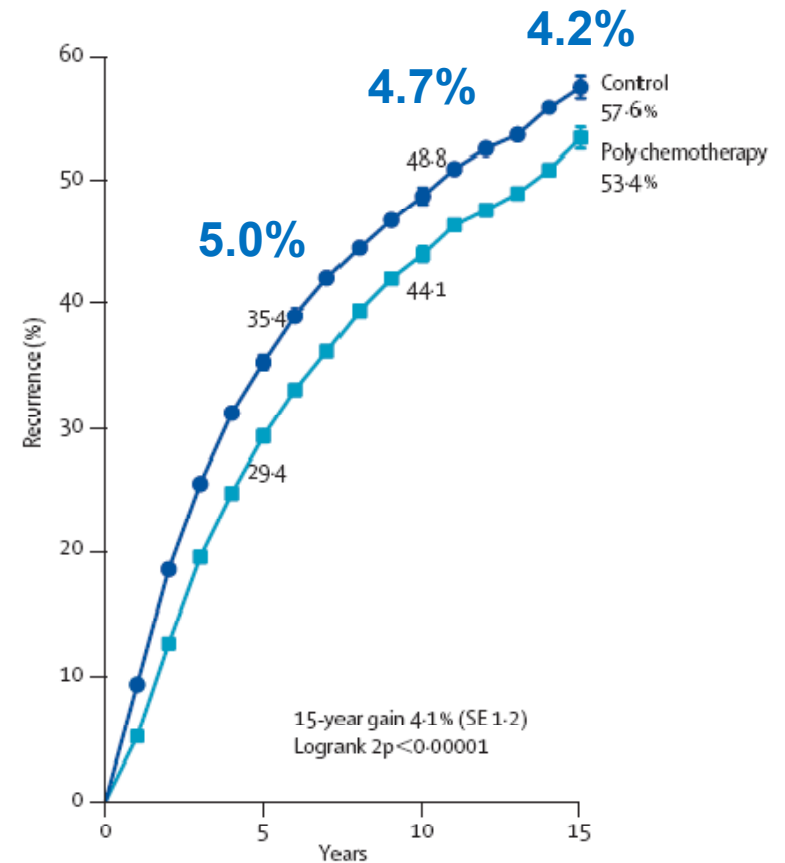
- Premenopausal?
- Tumor size
- Grade 3
- N+

# The Impact of Chemotherapy on Recurrence Is Seen in Years 0-5

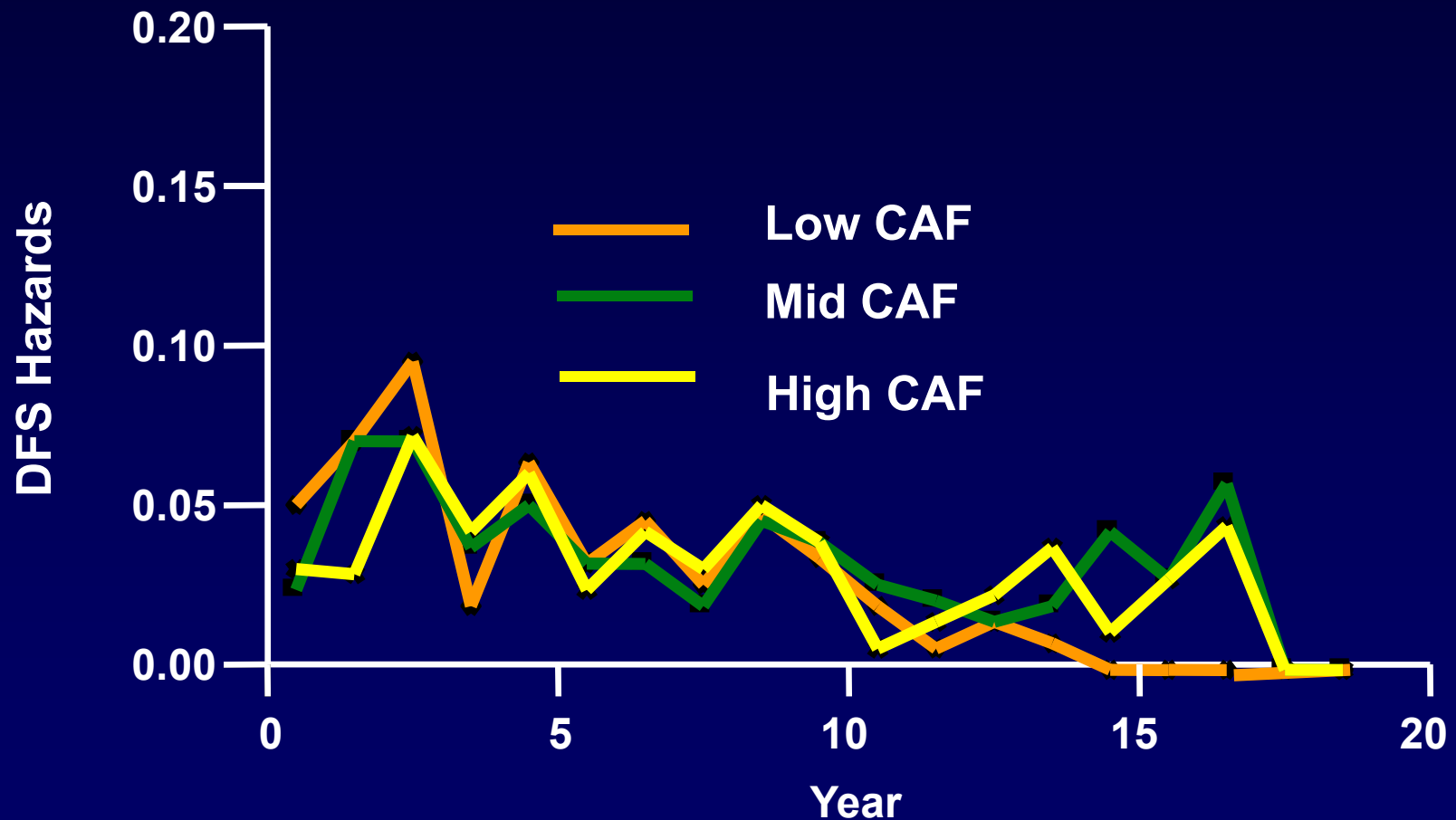
Entry age <50 years: recurrence



Entry age 50-69 years: recurrence



# Long-Term Outcome in ER-Positive Breast Cancer (CALGB Study 8541)



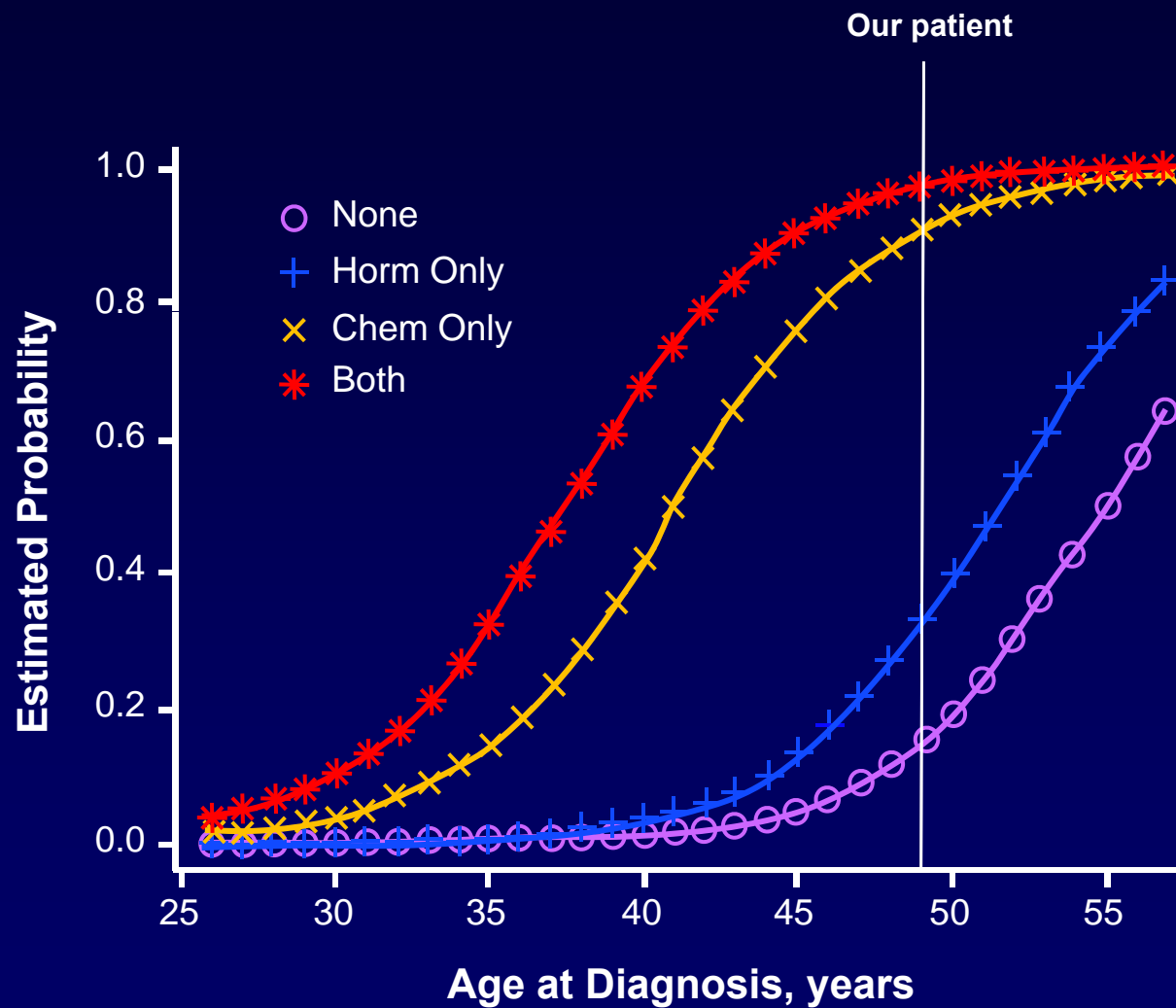
**How would you evaluate this  
amenorrheic patient's current  
menopausal status?**

# Rates of Chemotherapy-Induced Amenorrhea

Agents	“Younger” Women ( $\leq 40$ y)	“Older” Women ( $>40$ y)
Alkylating	18% to 61%	61% to 97%
Anthracyclines	~ 32%	~ 88%
Taxanes (+A)	~ 61%	~ 84%

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# Mathematical Model of Risk of Menopause: First Year After Diagnosis



## Use of AIs in Perimenopause: Royal Marsden Experience

45 women, median age 47 (39-52) years with chemotherapy-induced amenorrhea and treated with AIs (33 biochemically confirmed ovarian suppression)

- Recovery of ovarian function: 12 (27%)
- Pregnancies 1
- Median duration of amenorrhea: 12 (4-59) months
- Median time on AI: 6 (3-18) months

# Biochemical Monitoring of Ovarian Function in Perimenopause

- **Single measurement of FSH, (LH), E<sub>2</sub>, beta inhibin reflects function only at that time point, but is not predictive**
- **Tests used for E<sub>2</sub> measurements are highly unreliable in perimenopause, as they do not extract or purify E<sub>2</sub> from plasma**
- **Measurement in patients receiving a steroidal AI cross-react even with most specialized immunoassays**

FSH, follicle-stimulating hormone; LH, luteinizing hormone

Smith IE, et al. *J Clin Oncol*. 2006;24(16):2444-2447.

# Tamoxifen Efficacy Does Not Differ Significantly According to Patient Age

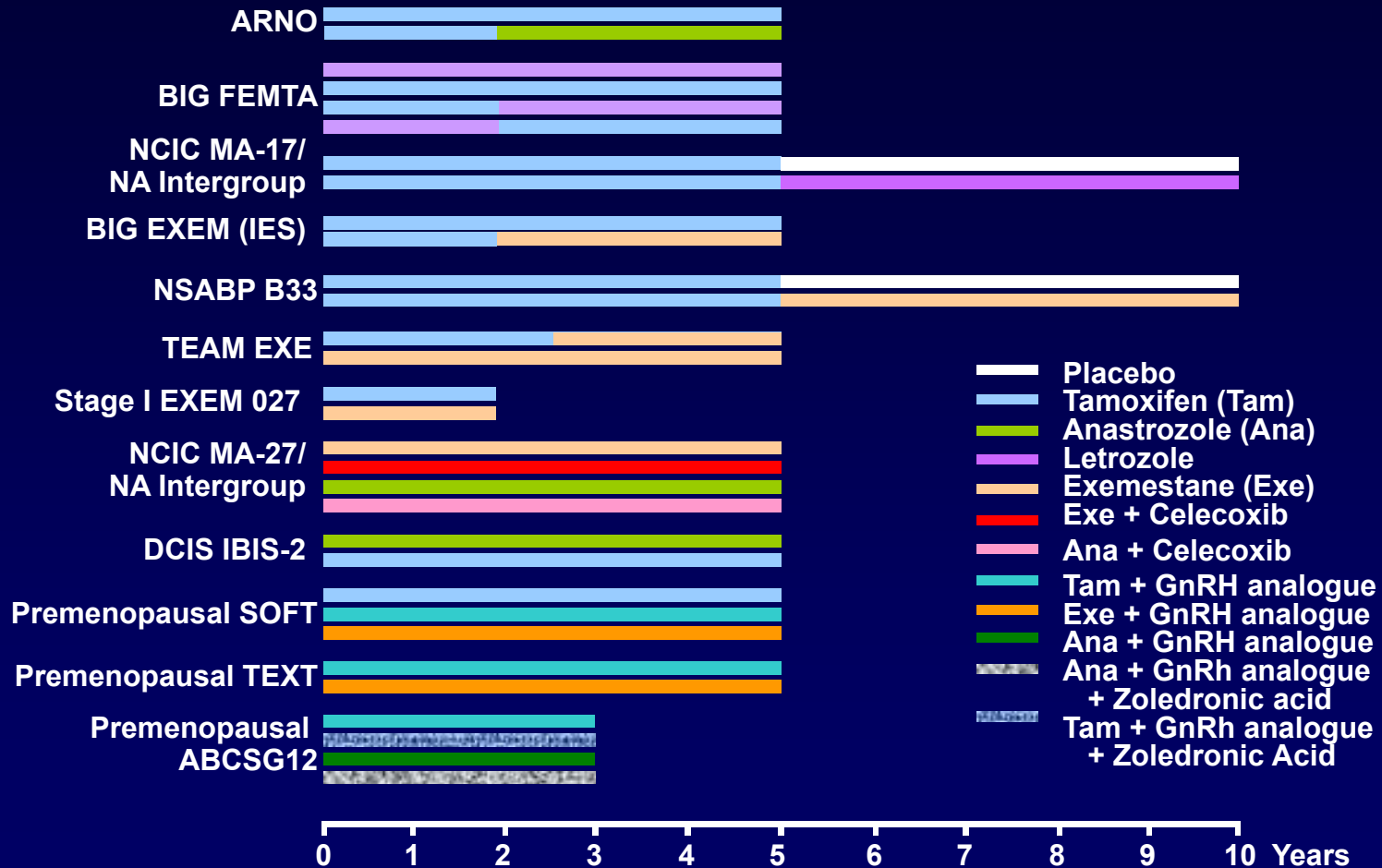
	Annual Risk Ratio $\pm$ SE			
	Breast Cancer Recurrence Rate		Breast Cancer Death Rate	
	Risk Ratio	SE	Risk Ratio	SE
For all age groups	0.59	0.03	0.66	0.04
Age, years				
<40	0.56	0.10	0.61	0.12
40-49	0.71	0.07	0.76	0.09
50-59	0.66	0.05	0.76	0.07
60-69	0.55	0.05	0.65	0.06
$\geq 70$	0.49	0.12	0.63	0.15

Parton M, et al. *J Clin Oncol.* 2008;26(5):745-752 after Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet.* 2005;365(9472):1687-1717.

# If Use of AIs Is Considered in Perimenopause (Age <55 Years)

- **Serial monthly measurement of FSH and E<sub>2</sub>**
  - For at least 6 months
  - For AI after tamoxifen situation even longer
- **If E<sub>2</sub> remains >10 pmol/L = AI is not fully effective**
  - Switch back to tamoxifen
  - Surgical ovarian ablation
- **Instruct patients to contact clinician if menstrual bleed recurs or hot flushes stop abruptly**
- **Adequate contraception should be practiced during monitoring period**
- **Anti Müllerian Hormone (AMH) is most reliable indicator of residual follicular function**

# Adjuvant Therapy Trials of Aromatase Inhibitors

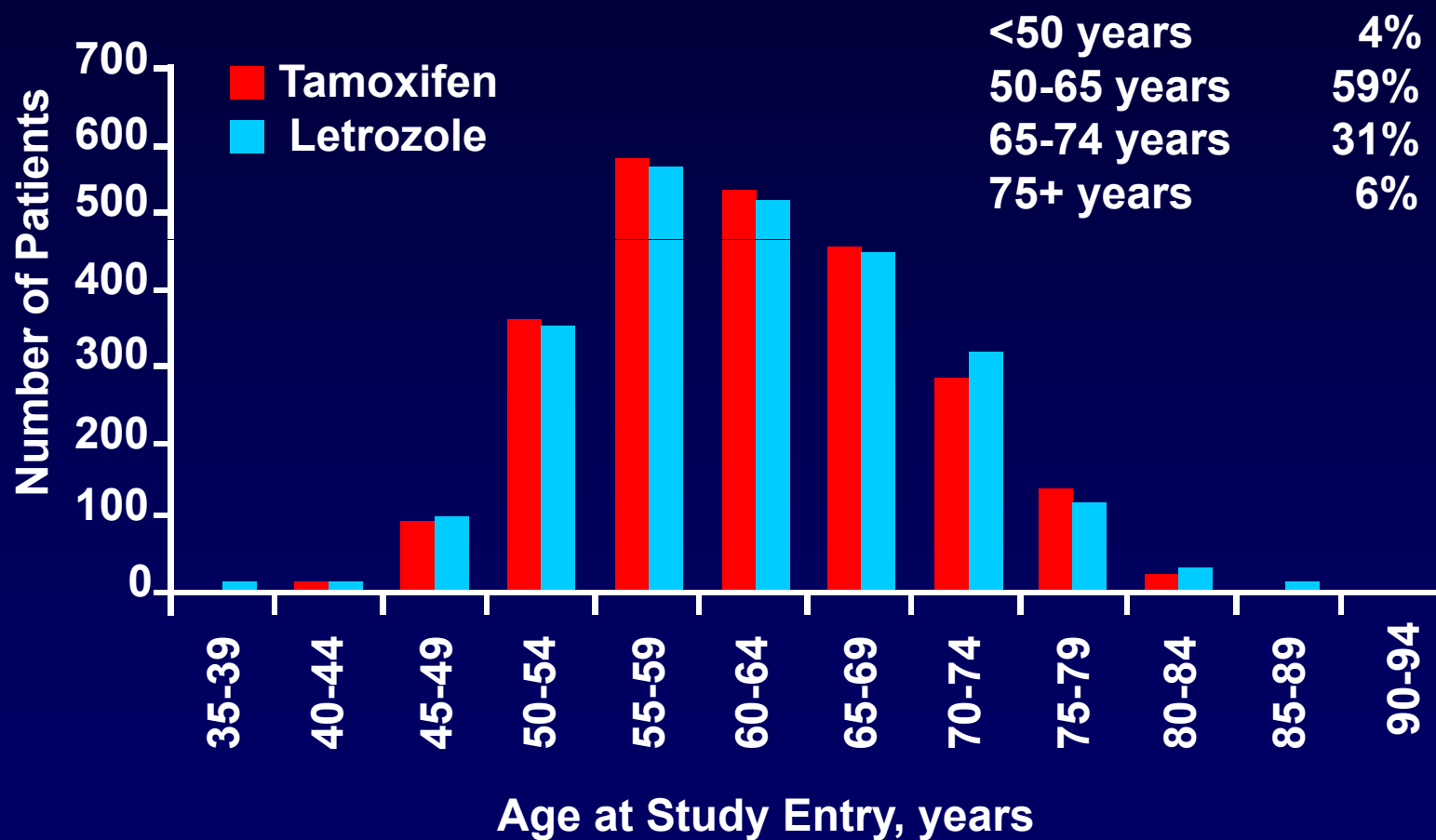


**Most studies exclude women of uncertain menopausal status**

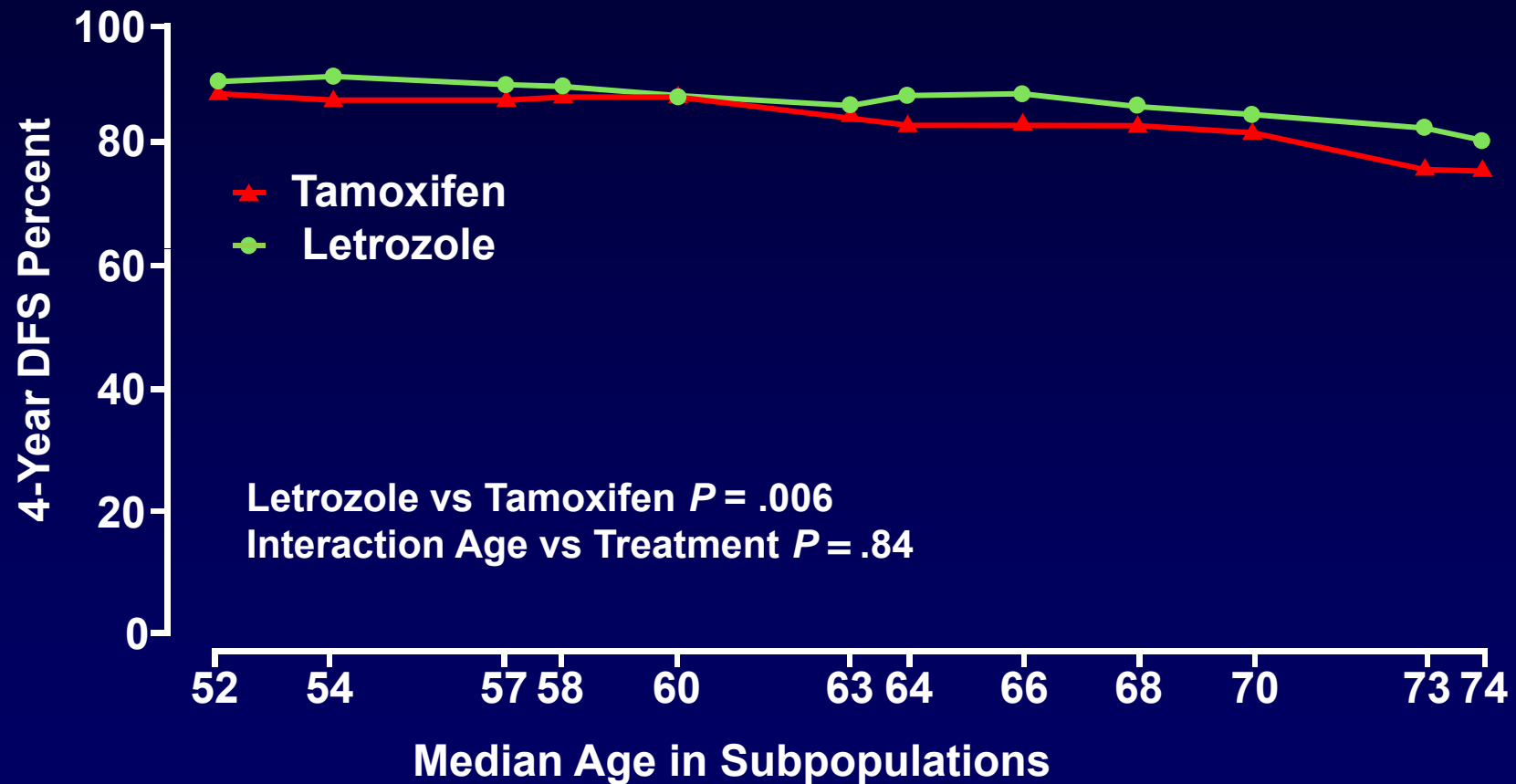
# How Does Age Influence Als vs Tamoxifen?

- **BIG 1-98**
- **5 Years letrozole vs tamoxifen arms**
- **4922 patients**
- **Median follow-up 40 months**

# BIG 1-98 Letrozole vs Tamoxifen Age Distribution



# BIG 1-98 Letrozole vs Tamoxifen STEPP\* Analysis 4-Year DFS



\*Subpopulation Treatment Effect Pattern Plots  
DFS = disease-free survival

Crivellari D, et al. *J Clin Oncol*. 2008;26(12):1972-1979.

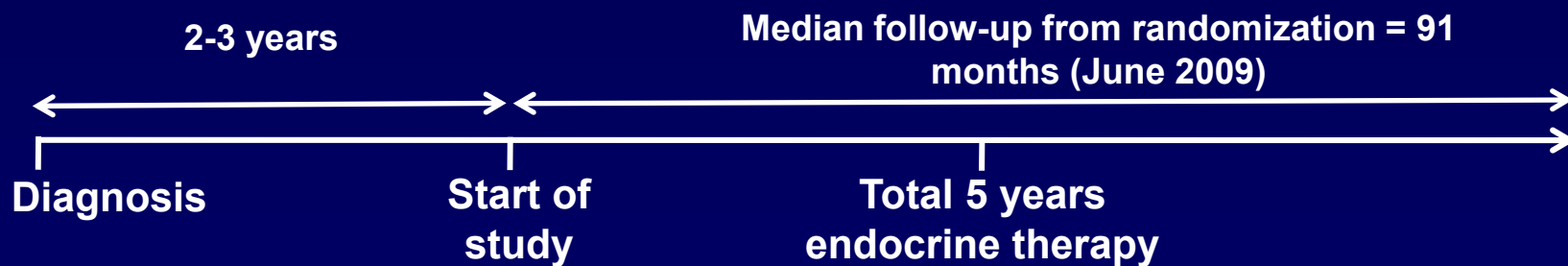
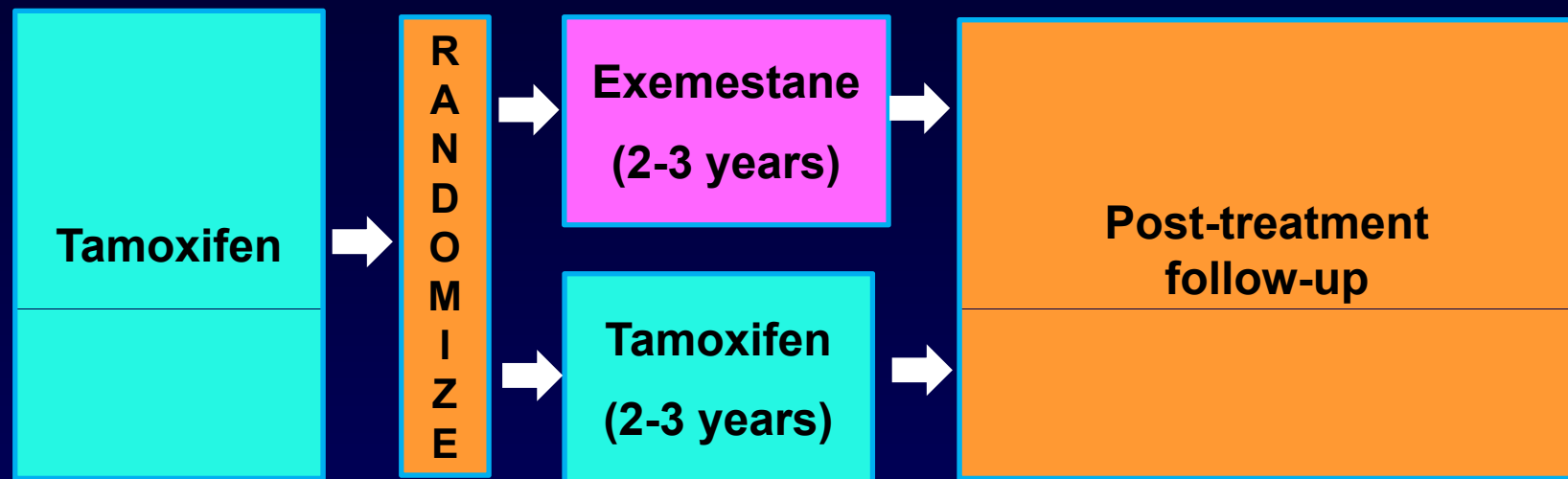
# Predictors for Early Relapse AI vs Tamoxifen (BIG 1-98)

- **Node positivity\***  $P < .001$
- **ER and PR neg**  $P < .001$
- **Grade 3 tumor**  $P < .001$
- **HER2 positivity**  $P < .001$
- **Large tumor size\***  $P = .001$
- **Treatment with tamoxifen**  $P = .002$
- **Vascular invasion\***  $P = .02$

\* tendency for higher efficacy with letrozole

**Based on your evaluation, patient is postmenopausal and completed 2 years of tamoxifen. What now?**

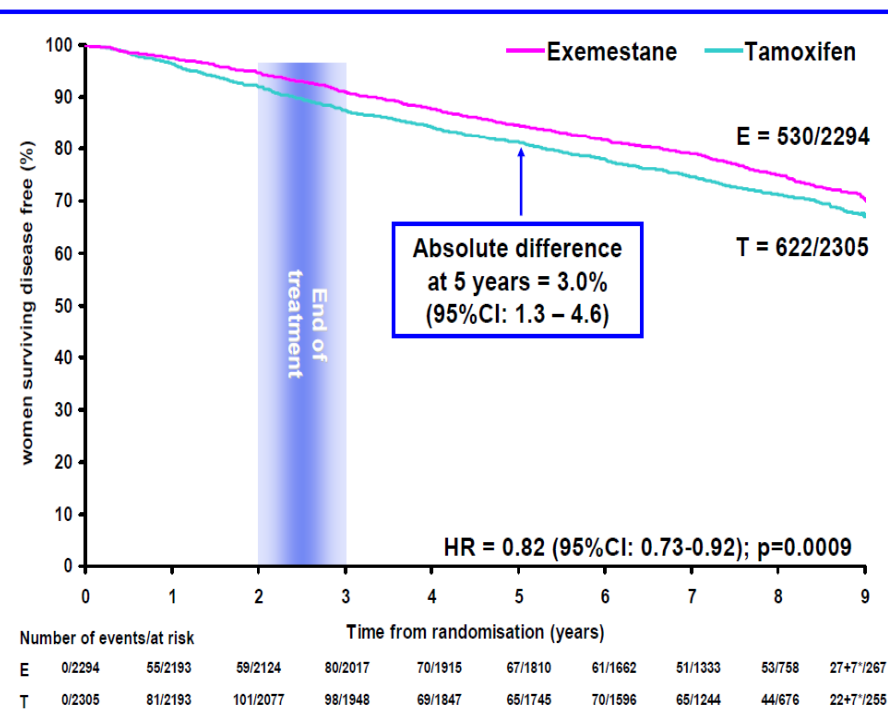
# Intergroup Exemestane Study: Trial Design



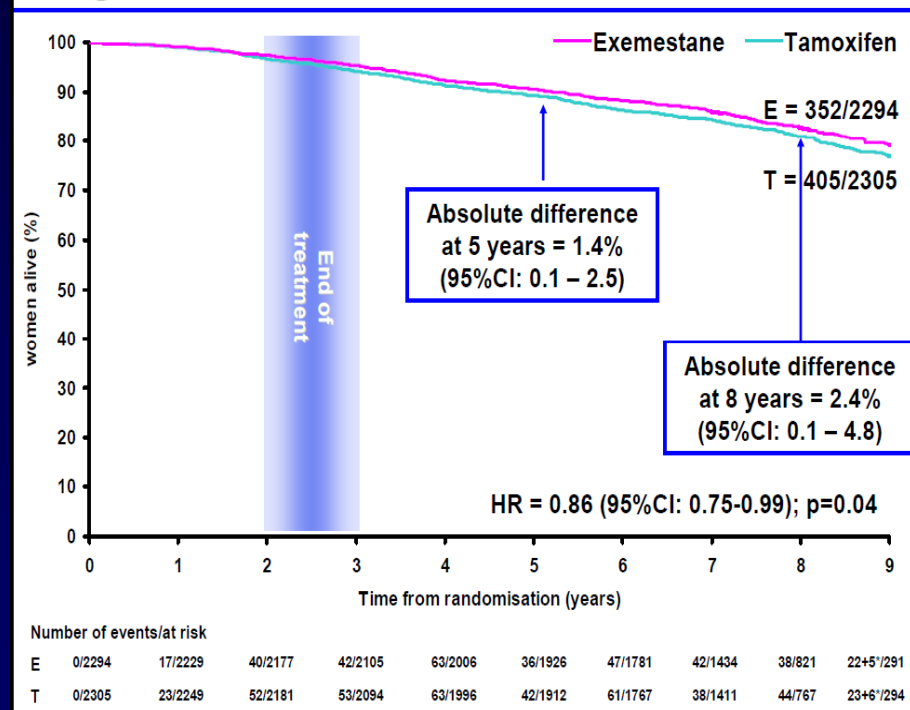
Total follow-up available from randomization at June 2009 analysis = 32296 women years

# IES Update: DFS and OS Median Follow-Up 91 Months

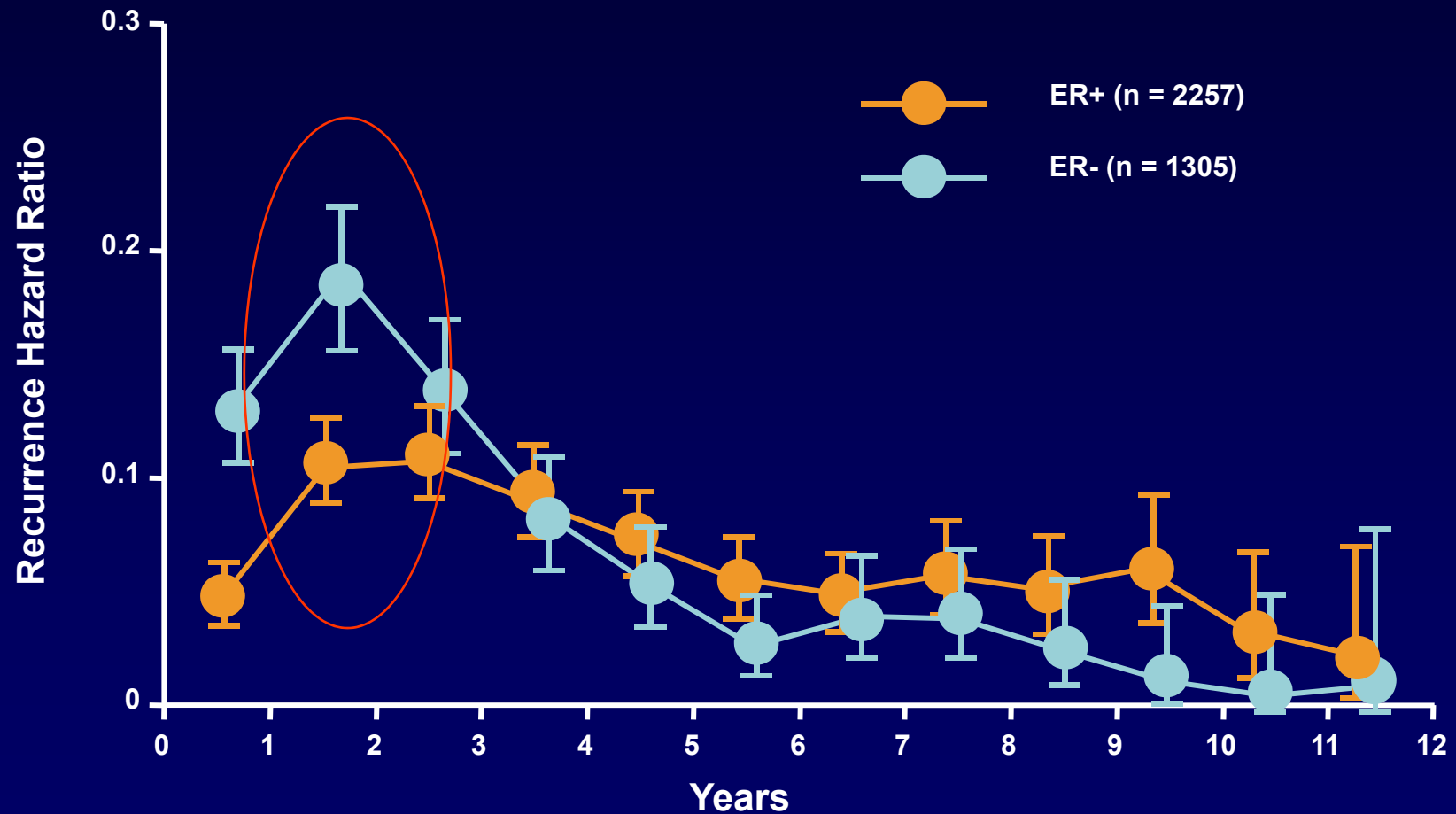
## Disease Free Survival – ER+/unknown



## Overall survival – ER+/unknown



# Patterns of Recurrence After Breast Cancer Diagnosis: Analysis by Hormone-Receptor Status



# Extended Adjuvant Treatment: AI vs Placebo After 5 Years Tamoxifen

Trial	Treatment	N	Median Follow-Up	Hazard
MA17 <sup>1</sup>	Letrozole	5157	29	0.57
B-33 <sup>2</sup>	Exemestane	1562	30	0.44
ABCSG 6a <sup>3</sup>	Anastrozole	856	60	0.64

**Overall HR<sup>4</sup>: 0.56**

1. Goss P, et al. *J Natl Cancer Inst.* 2005;97(17):1262-1271. 2. Mamounas EP, et al. *J Clin Oncol.* 2008;26(12):1965-1971.  
3. Jakesz R, et al. *J Clin Oncol.* 2005;23(16S): Abstract 527. 4. Cuzick J, et al. *J Clin Oncol.* 2007;25(18S): Abstract 541.

# Are There Clinically Significant Differences Between the AIs as Adjuvant Therapy?

- **FACE**  
(Femara vs Anastrozole Clinical Evaluation)
  - **Letrozole vs anastrozole**
  - 4000 N+ve patients
- **MA-27**  
(NCIC / Intergroup)
  - **Exemestane vs anastrozole**
  - 6800 patients
- **GIM-3-FATA (Italian Breast Cancer Group)**
  - **Adjuvant trial of all AI (upfront vs switch after 2y of TAM)**
  - n = 10,000

**And if she was premenopausal...**

# ABCESG-12 Trial Design

- Accrual 1999-2006
- 1803 premenopausal patients with breast cancer
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years

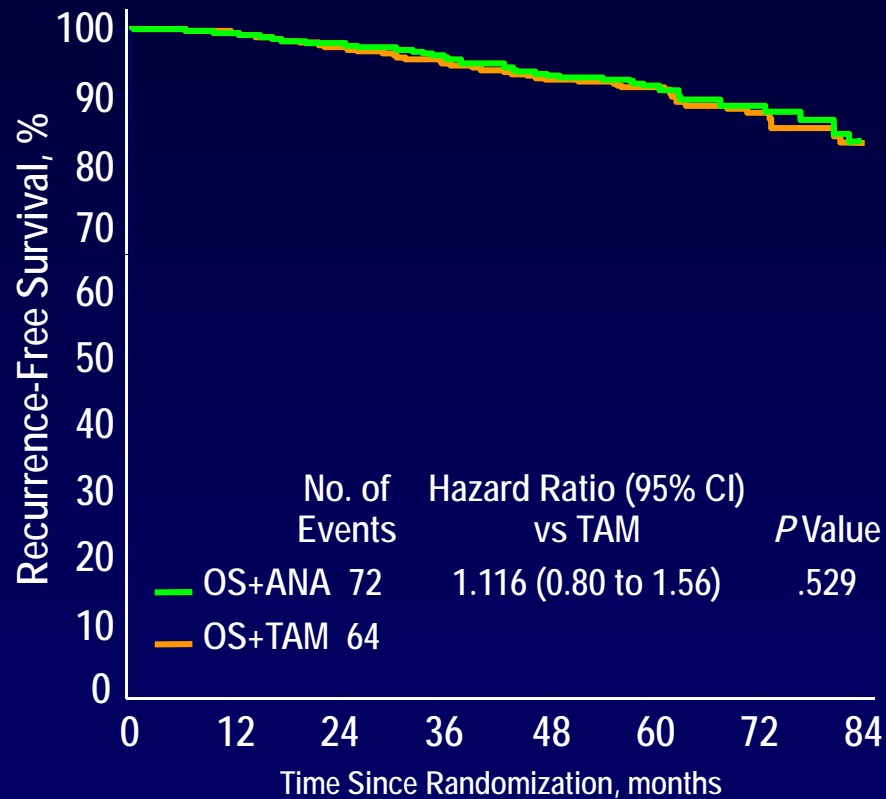


ABCESG-12 = Austrian Breast and Colorectal Cancer Study Group Trial 12.

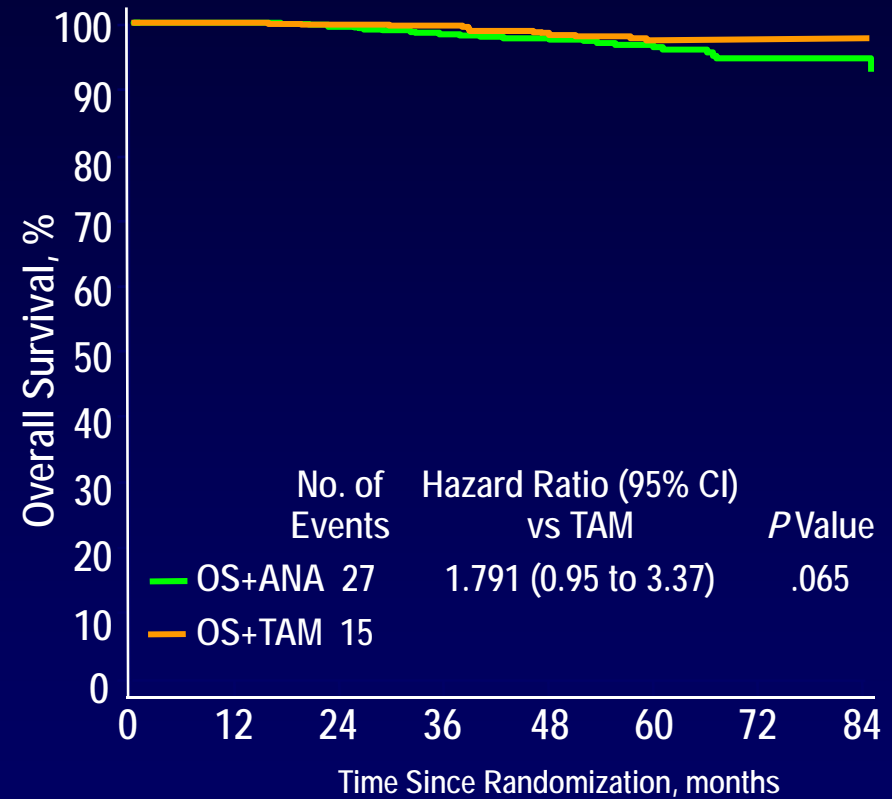
Gnant M, et al. *N Engl J Med.* 2009;360(7):679-691.

# Effects of Endocrine Strategies on Disease Outcomes

## Relapse-Free Survival



## Overall Survival



### Number at risk

	0	12	24	36	48	60	72	84
TAM	900	834	719	553	411	243	129	50
ANA	903	844	725	540	411	255	139	51

	0	12	24	36	48	60	72	84
TAM	900	840	736	580	439	264	141	60
ANA	903	849	743	558	436	271	151	59

# Suppression of Ovarian Function Trial (SOFT): Study Design

Target accrual: 3000

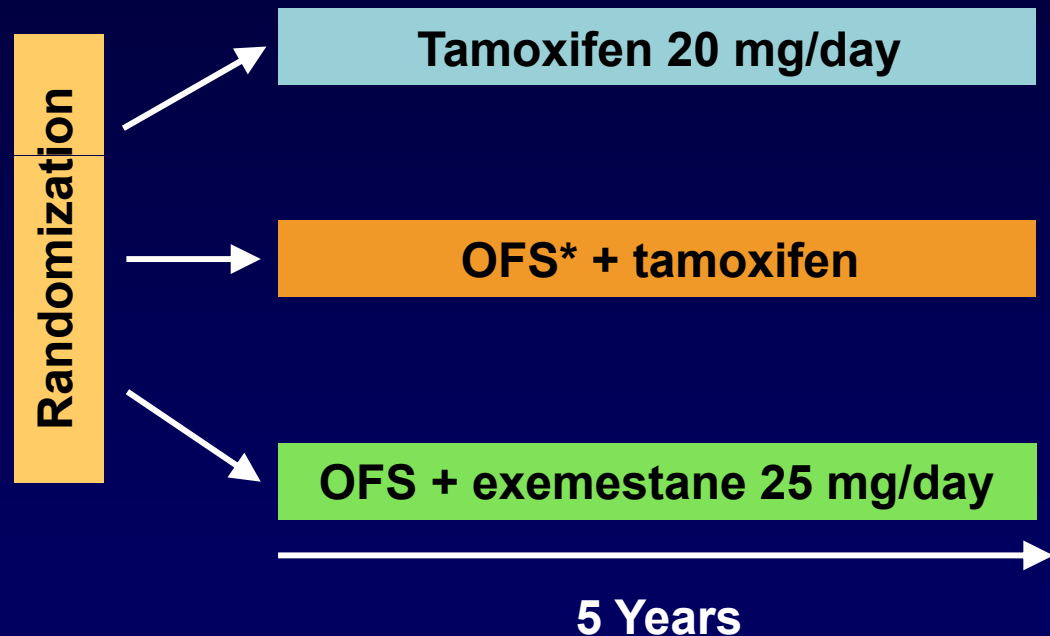
Enrolled as of 06/09: 2387

Eligibility:

Premenopausal

Estradiol (E<sub>2</sub>) in the premenopausal range either after or without chemotherapy

ER ≥ 10% and/or PgR ≥ 10%



\*OFS = ovarian function suppression using triptorelin 3.75 mg by injection every 28 days for 5 years from randomization x 5 years or surgical oophorectomy or ovarian irradiation.

Study Chairs: Prudence Francis, MD, and Gini Fleming, MD

# Tamoxifen and Exemestane Trial (TEXT): Study Design

Target accrual: 2639

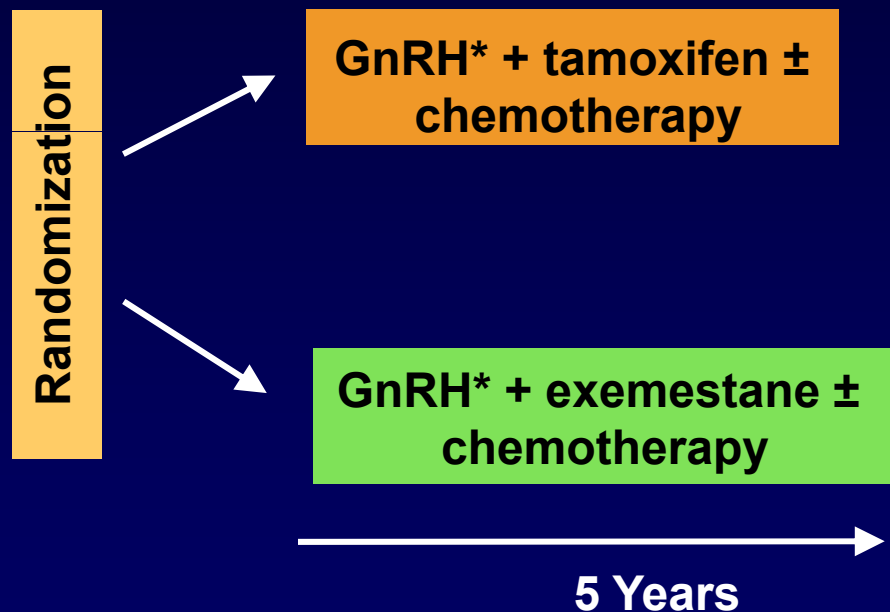
Enrolled as of 06/09: 2061

Eligibility:

Premenopausal

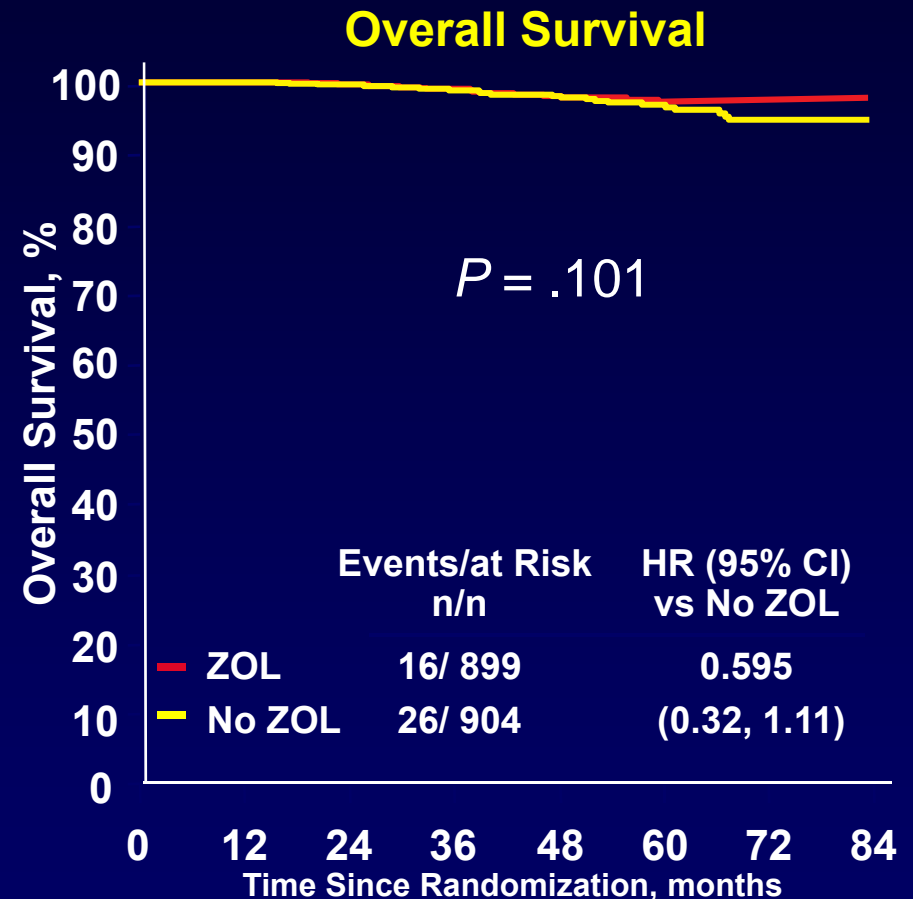
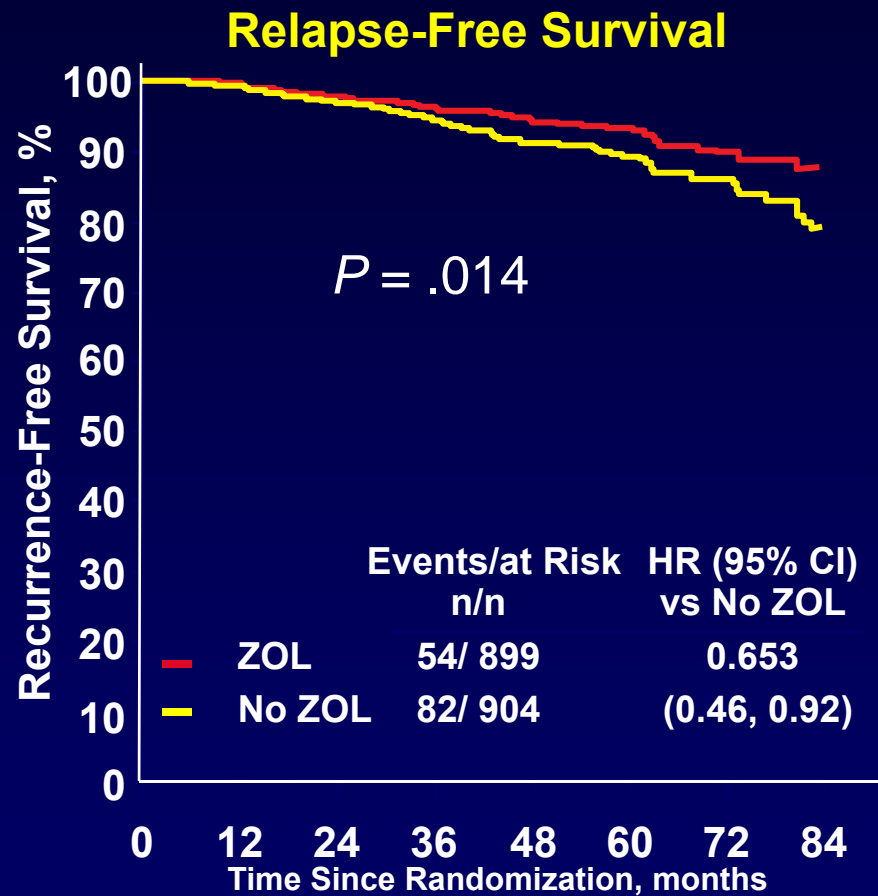
ER  $\geq$  10% and/or PgR  $\geq$  10%

Candidates to begin GnRH analogue from the start of adjuvant therapy



\*GnRH = triptorelin 3.75 mg by injection every 28 days for 5 years, but oophorectomy or radiation is allowed after 6 months.

# Effects of Zoledronic Acid on Disease Outcomes



#### Patients at risk

No ZOL	904	832	714	538	408	241	145	47
ZOL	899	846	730	555	414	257	123	54

904	838	735	565	441	265	161	60
899	851	744	573	434	270	131	59

# My Opinion

- Would check if **FSH** and E<sub>2</sub> are in postmenopausal range
- If postmenopausal, would switch to exemestane