



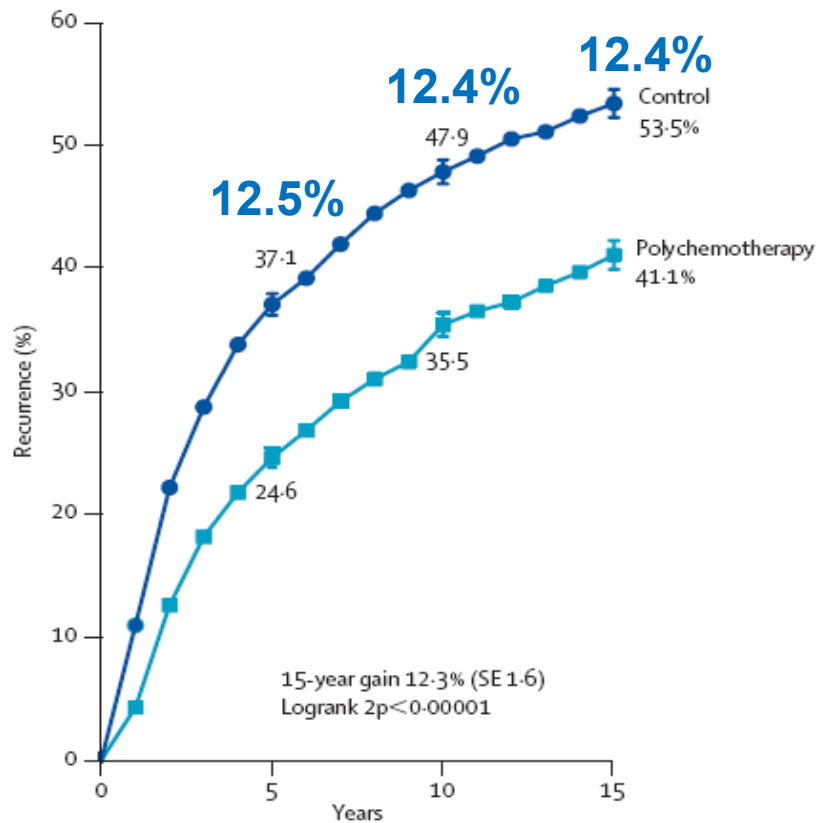
The  
University  
Of  
Sheffield.

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

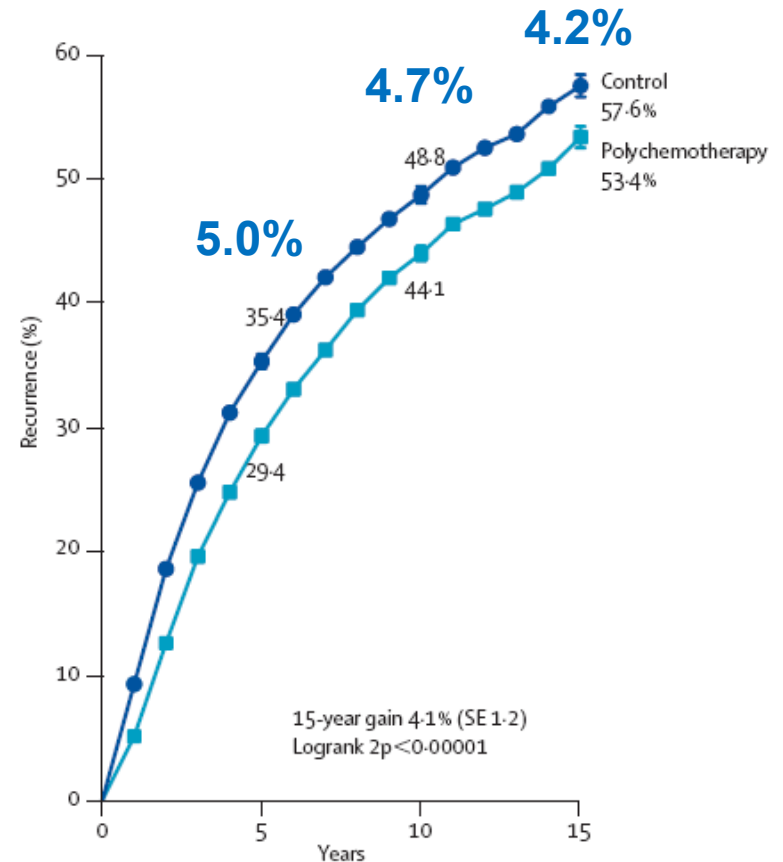
**Prof. Robert Coleman, MD**  
Cancer Research Centre  
Weston Park Hospital  
Sheffield, United Kingdom

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

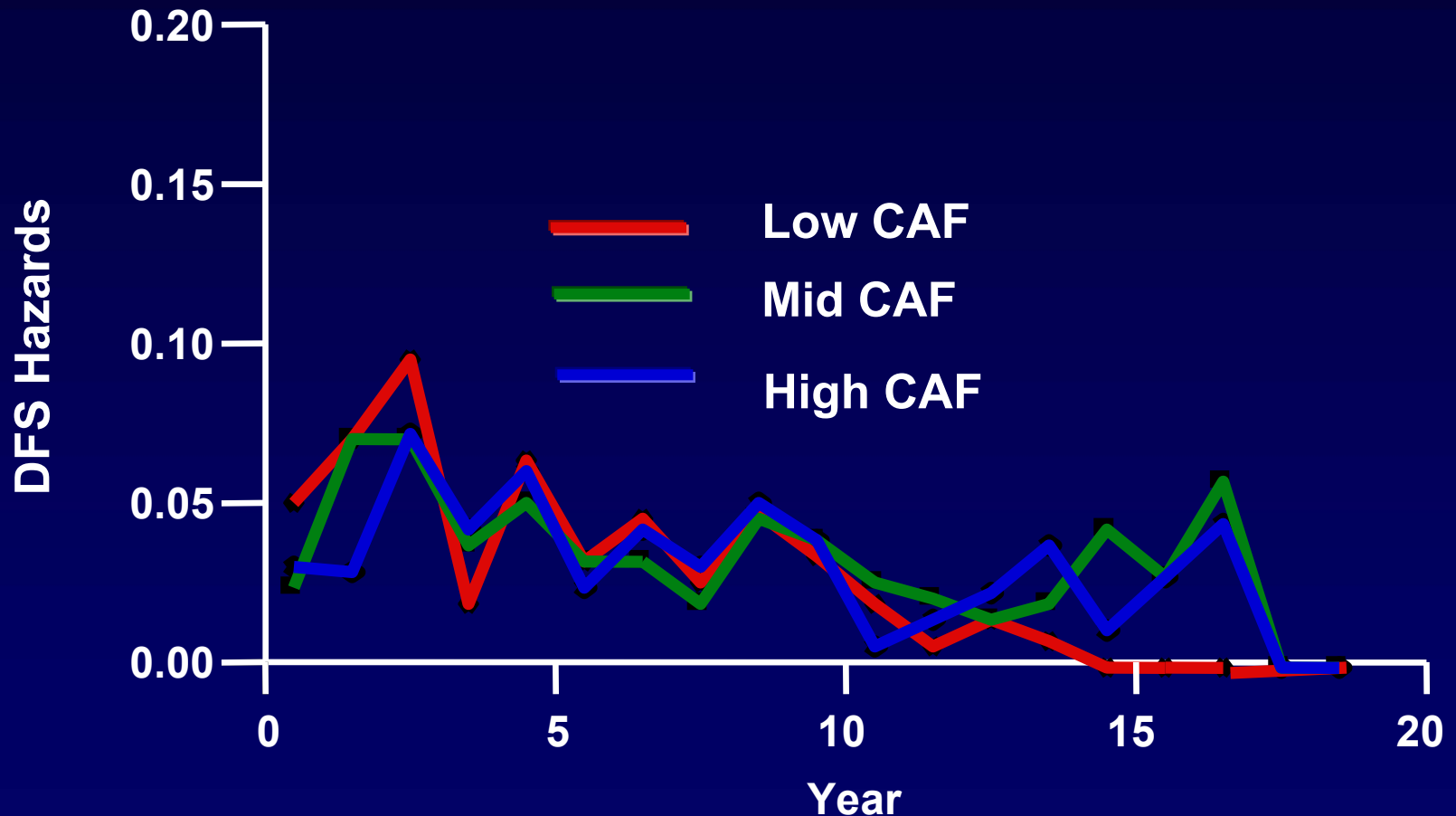
Entry age <50 years: recurrence



Entry age 50-69 years: recurrence



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

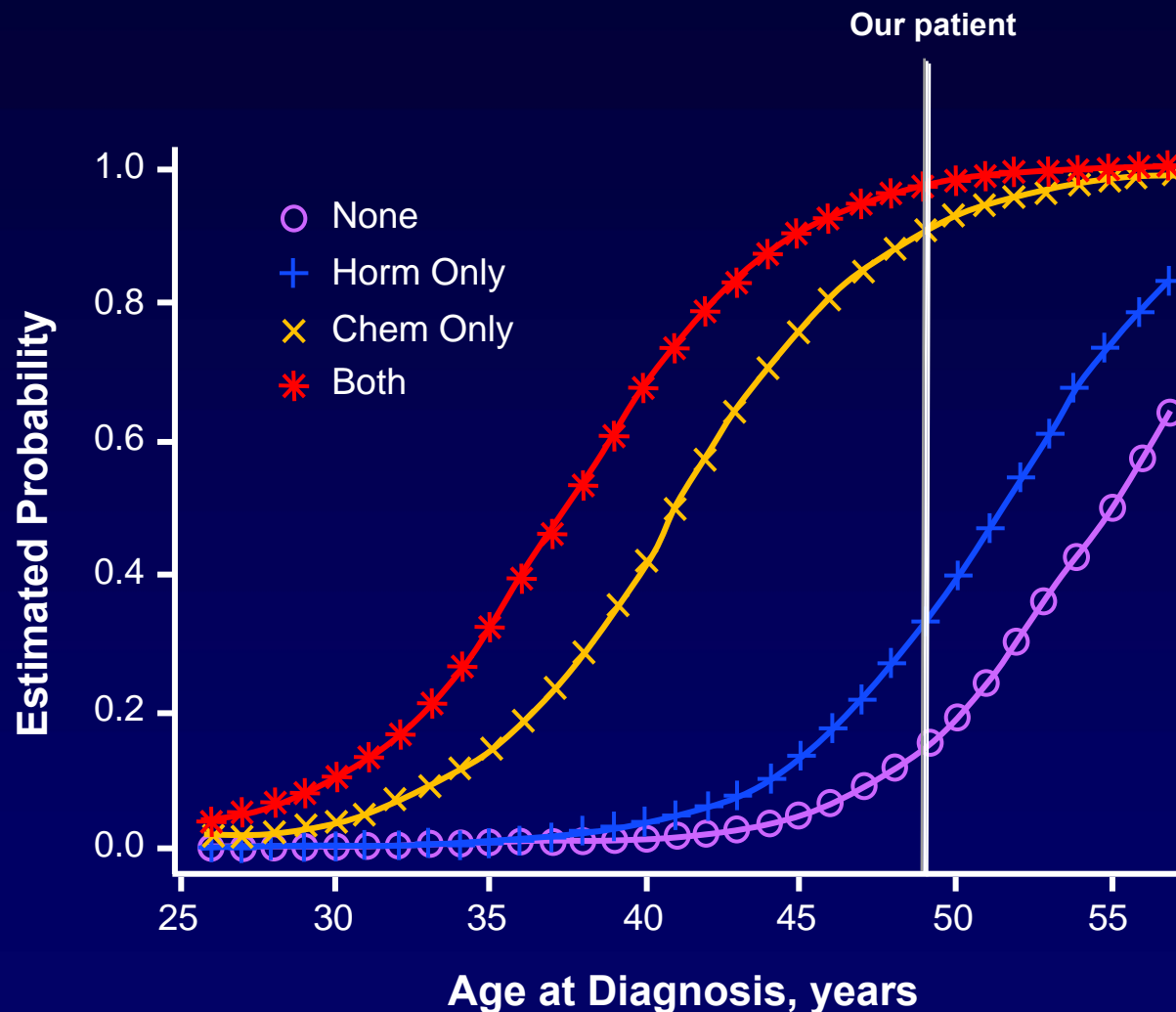


# Rates of Chemotherapy-Induced Amenorrhea

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



# Problems of Aromatase Inhibitor (AI) Use in the Perimenopausal Woman

- **Use of AI therapy in women with chemotherapy induced menopause may re-awaken ovarian function**
  - Pregnancies recorded
  - Menstruation may resume
  - Incomplete ovarian suppression may negate AI effects
- **Endocrine testing for menopause difficult**
  - Requires super-sensitive estradiol testing

**If in doubt, wait**

# 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

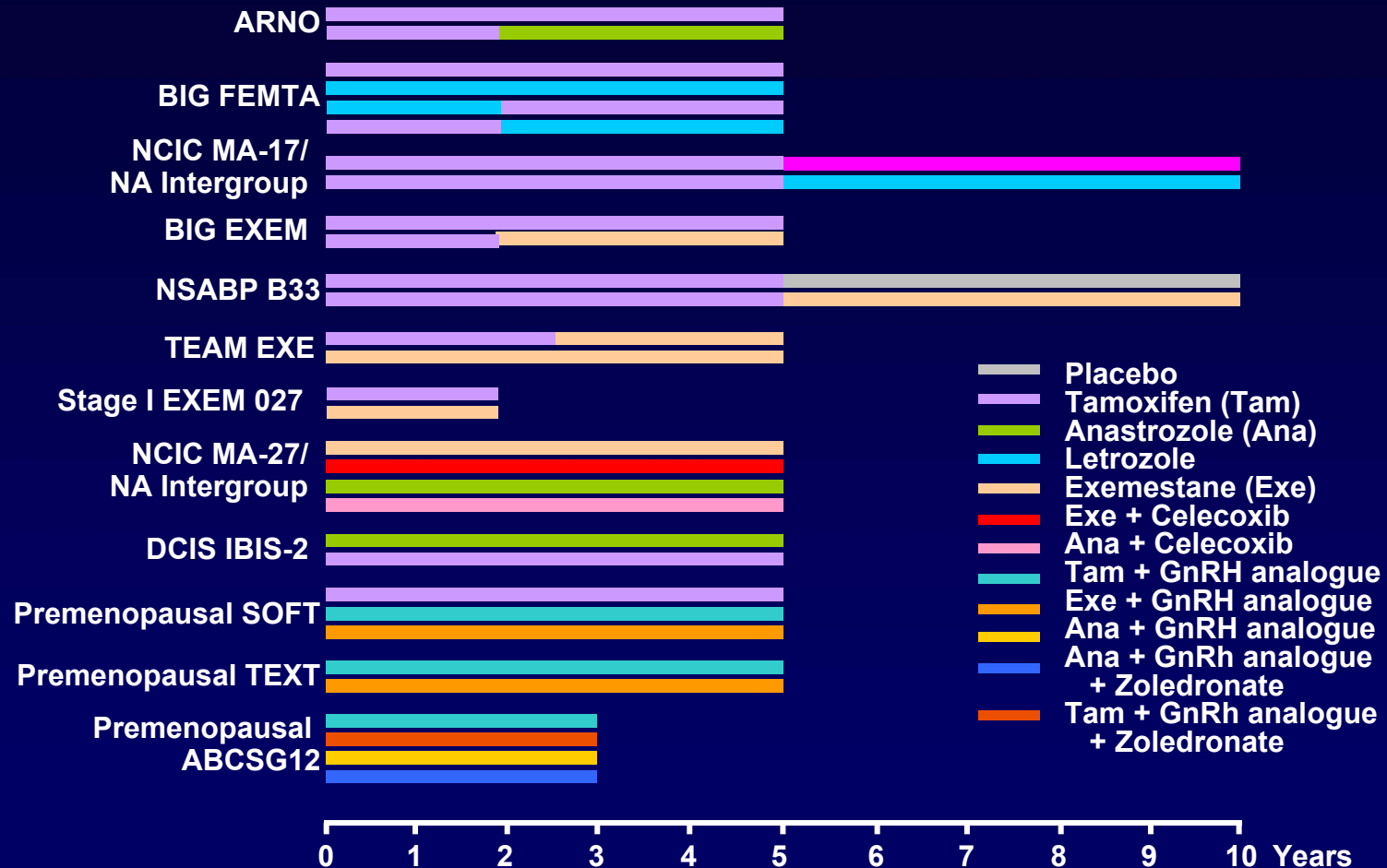
- **Single measurement of FSH, (LH), E<sub>2</sub>, beta inhibin reflects function only at that time point, but is not predictive**
- **Tests used for E<sub>2</sub> measurements are highly unreliable in perimenopause, as they do not extract or purify E<sub>2</sub> from plasma**
- **Measurement in patients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

FSH = follicle-stimulating hormone; LH = luteinizing hormone

# 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**

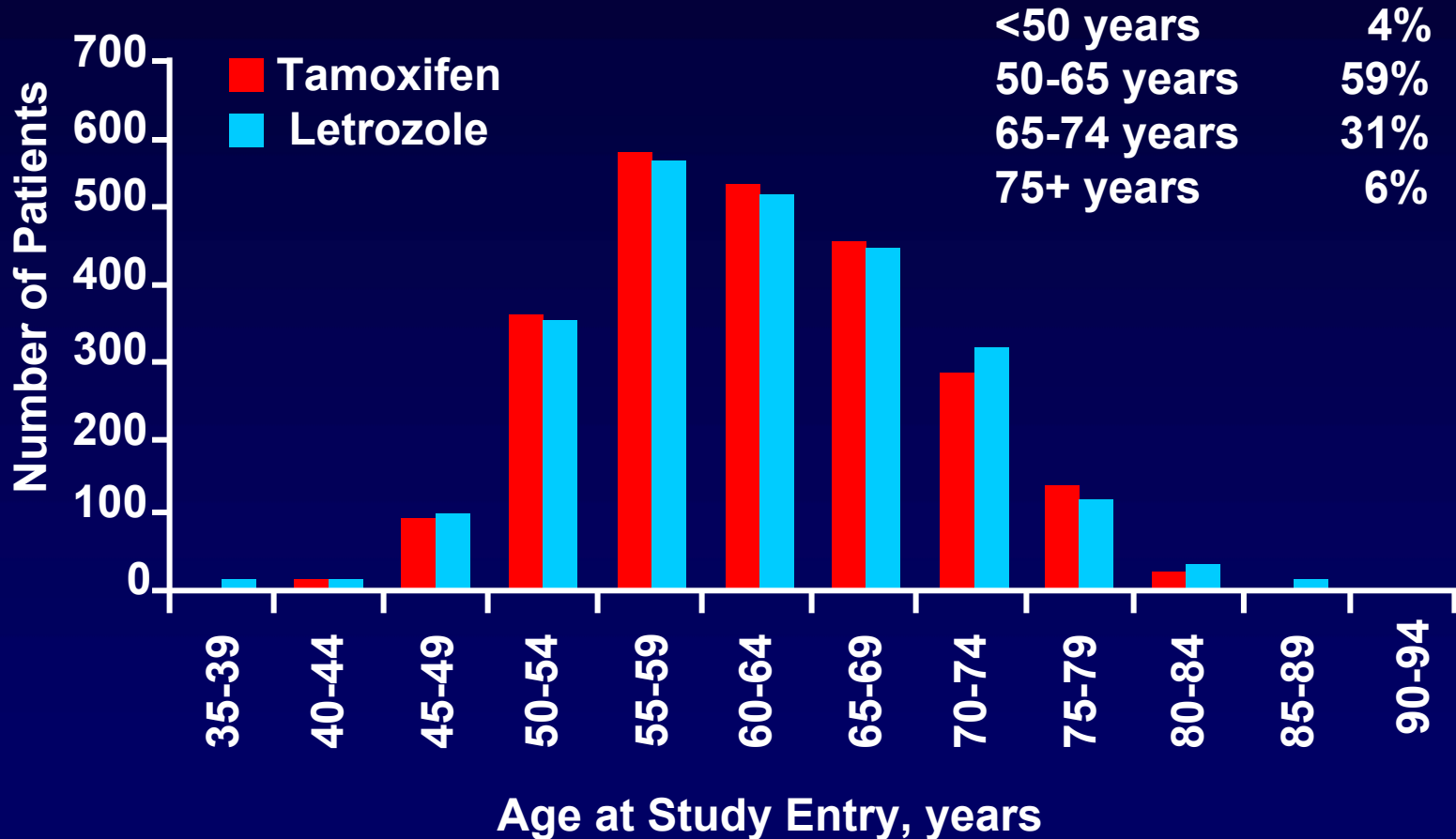
# Tamoxifen Efficacy Does Not Differ Significantly According to Patient Age

	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

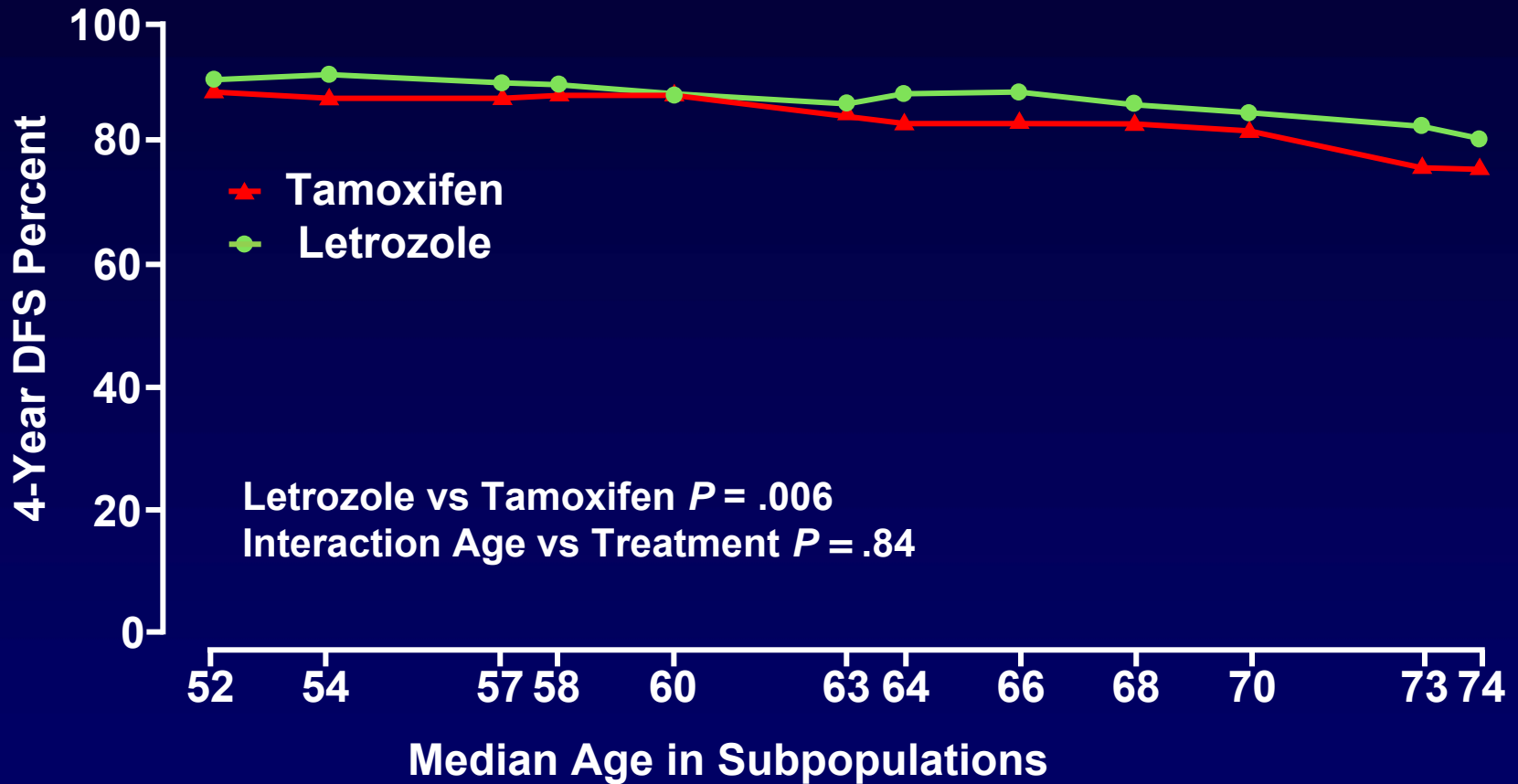
# How Does Age Influence Als vs Tamoxifen?

- **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



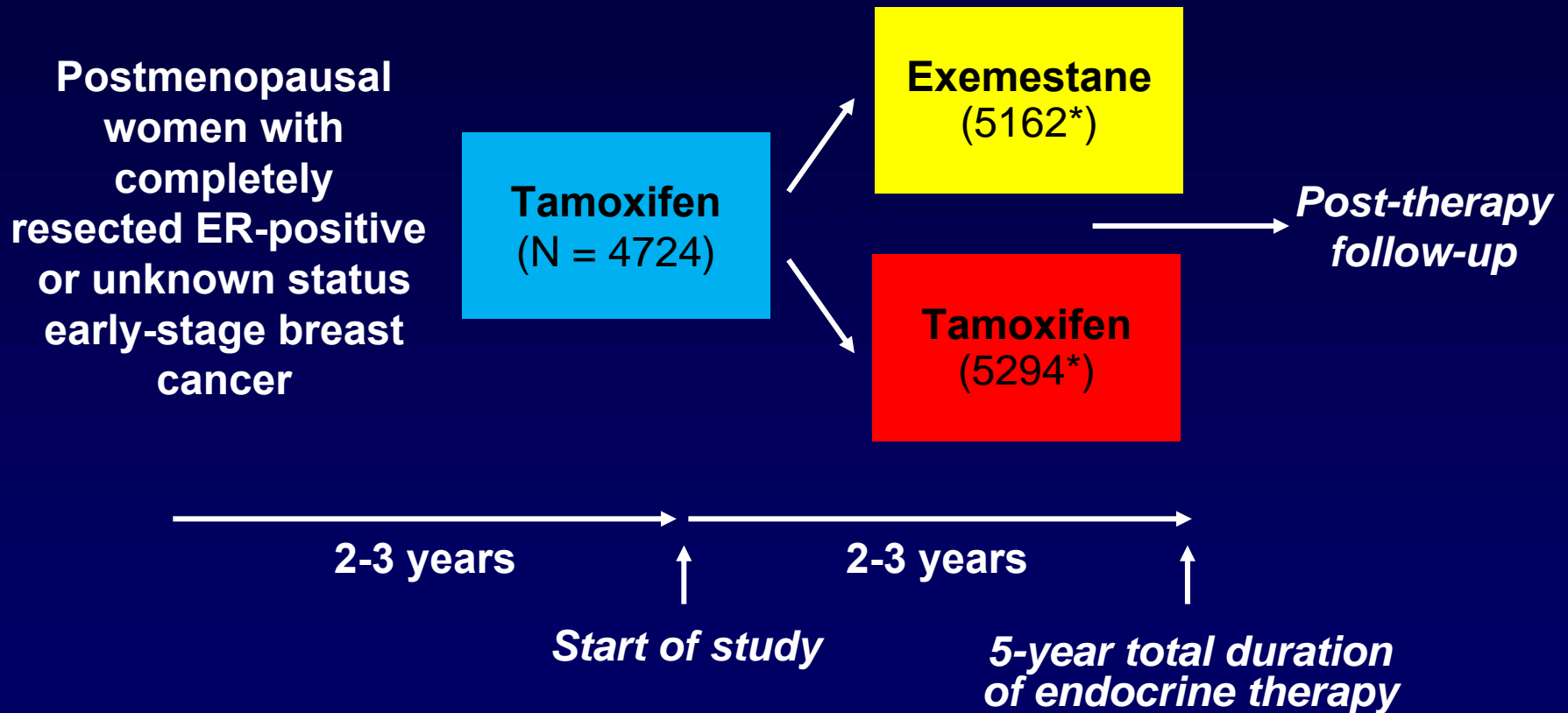
\*Subpopulation Treatment Effect Pattern Plots  
DFS = disease-free survival

# 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

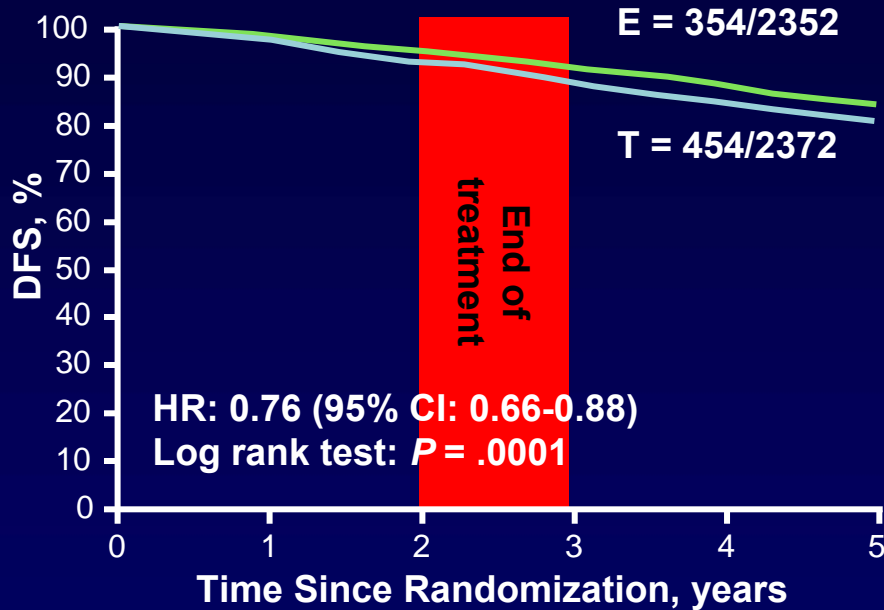
# Intergroup Exemestane Study: Trial Design



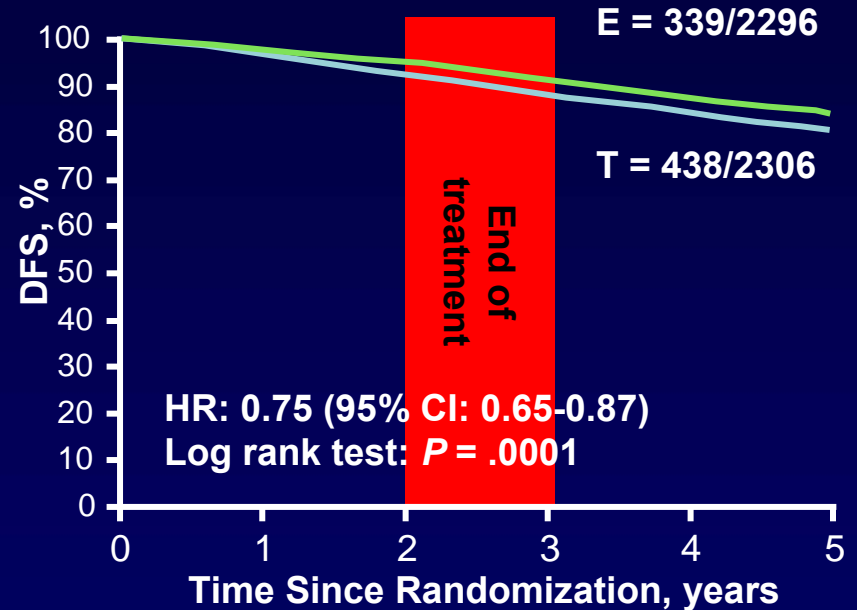
\*Total women-years

# Exemestane After Tamoxifen: DFS

## Intent-to-Treat



## ER+/Unknown

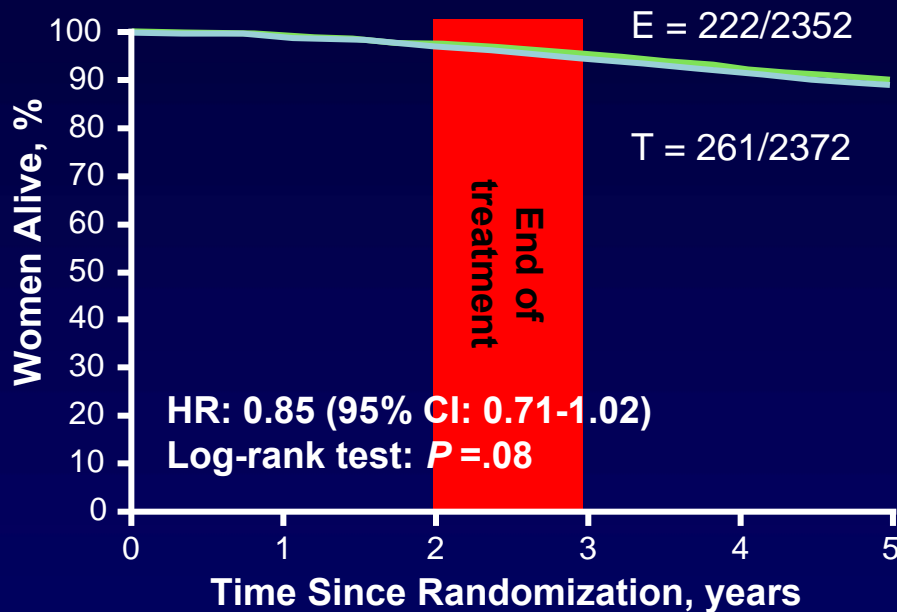


Year	2.5	5.0
Abs diff, % (95% CI)	3.2 (1.6-4.9)	3.4 (0.1-6.8)

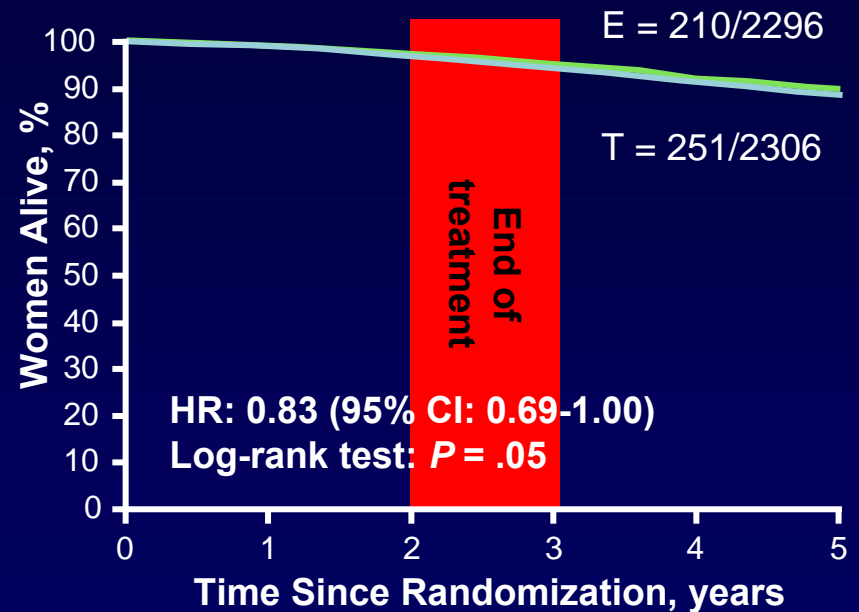
Year	2.5	5.0
Abs diff, % (95% CI)	3.4 (1.8-5.1)	3.5 (0.1-6.9)

# Exemestane After Tamoxifen: OS

## Intent-to-Treat



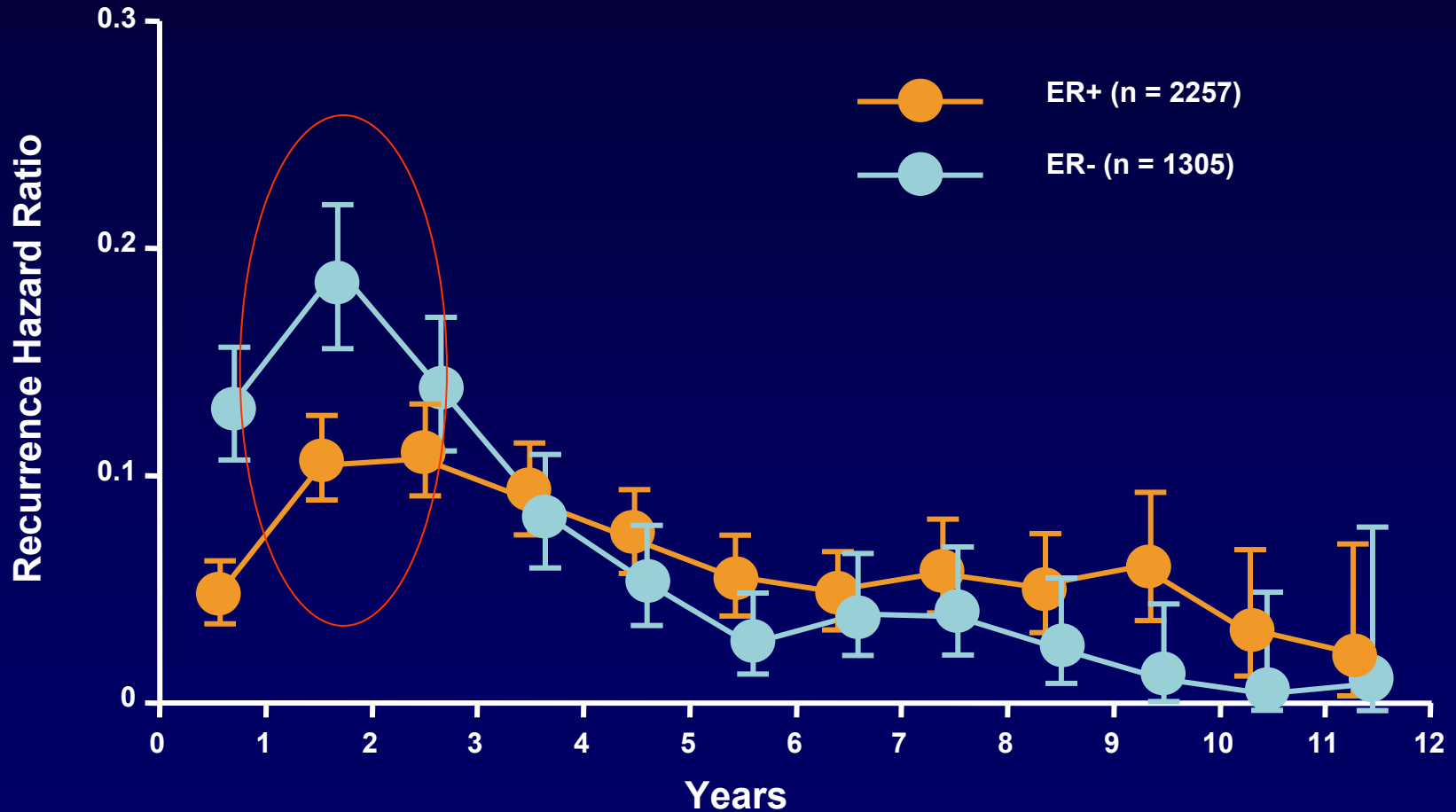
## ER+/Unknown



Year	2.5	5.0
Abs diff, % (95% CI)	0.8 (-0.4 to 1.9)	1.2 (-1.5 to 3.9)

Year	2.5	5.0
Abs diff, % (95% CI)	0.7 (-0.4 to 1.9)	1.6 (-1.2 to 4.3)

# 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

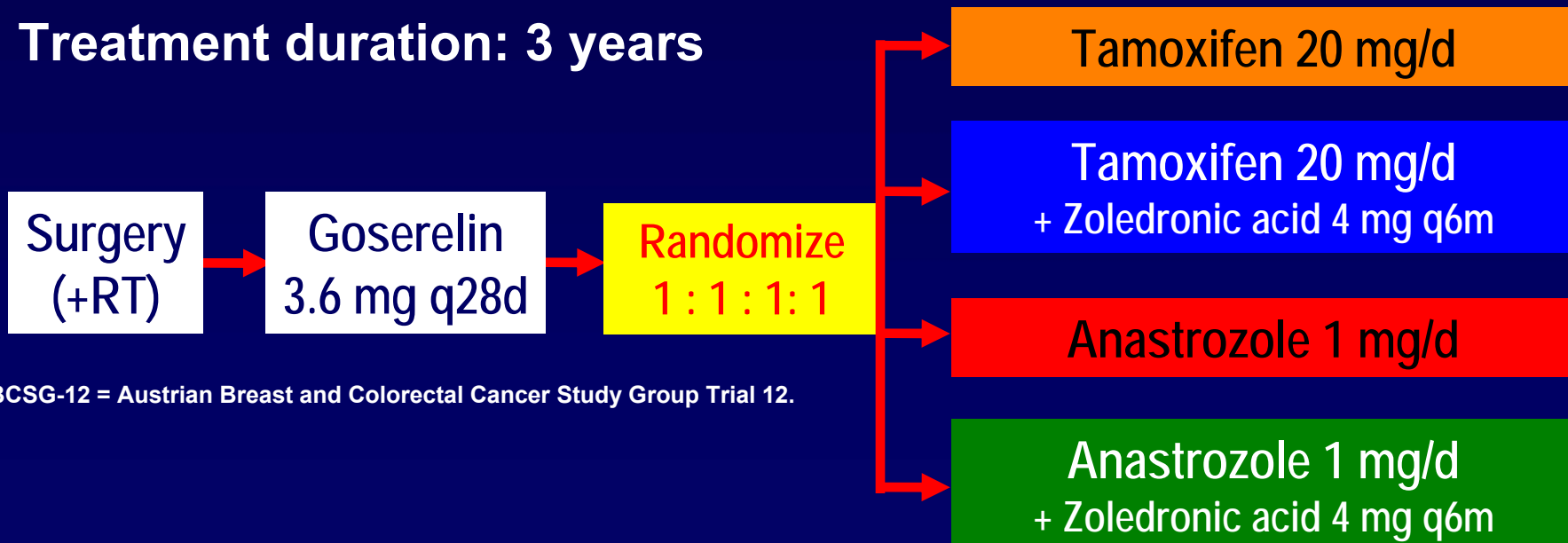
**Overall HR<sup>4</sup>: 0.56**

# 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

# ABCESG-12 Trial Design

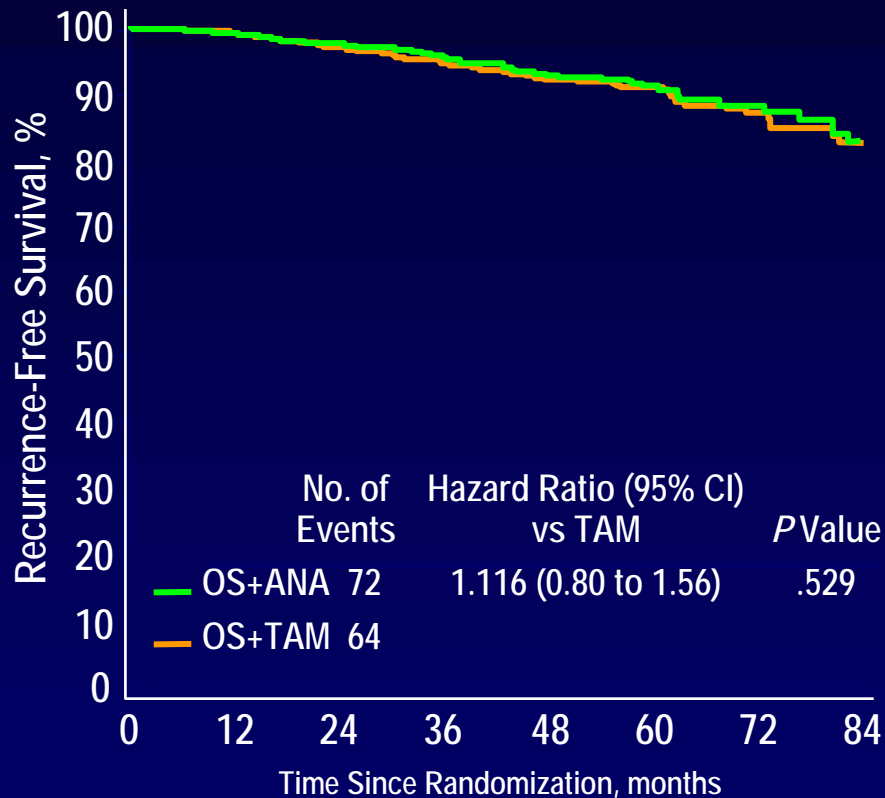
- Accrual 1999-2006
- 1803 premenopausal patients with breast cancer
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



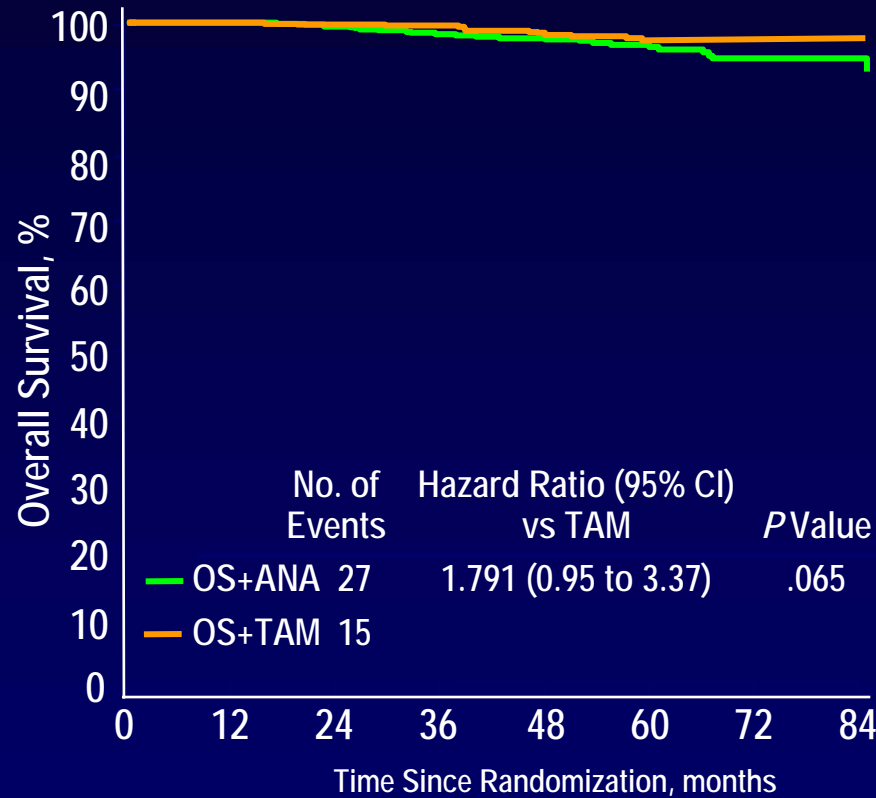
ABCESG-12 = Austrian Breast and Colorectal Cancer Study Group Trial 12.

# Effects of Endocrine Strategies on Disease Outcomes

## Relapse-Free Survival



## Overall Survival



### Number at risk

TAM	900	834	719	553	411	243	129	50
ANA	903	844	725	540	411	255	139	51

900	840	736	580	439	264	141	60
903	849	743	558	436	271	151	59

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

Target accrual: 3000

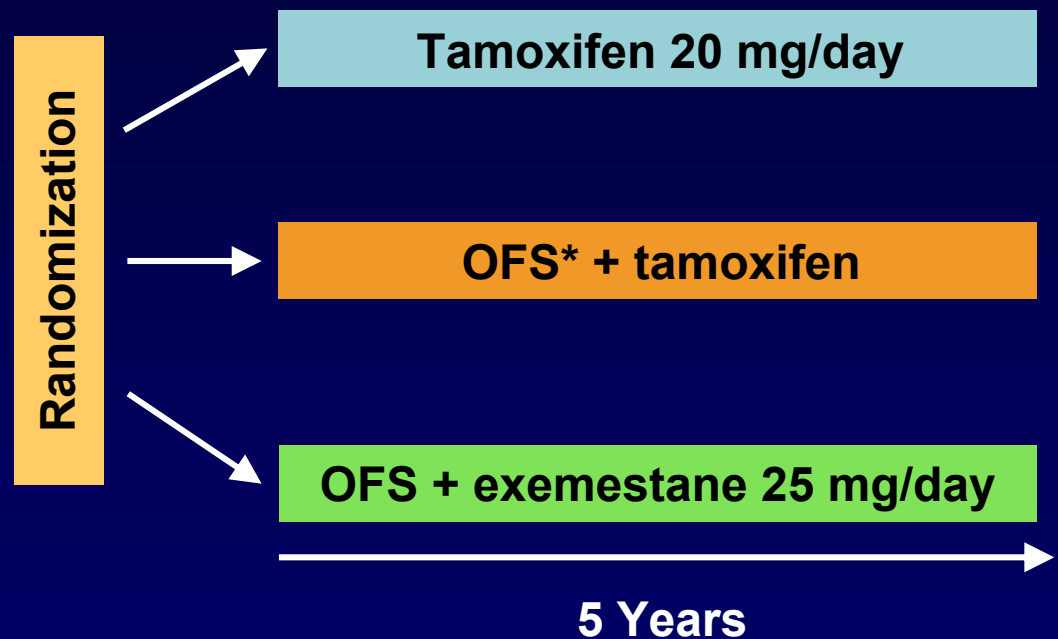
Enrolled as of 06/09: 2387

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.

# Tamoxifen and Exemestane Trial (TEXT): Study Design

Target accrual: 2639

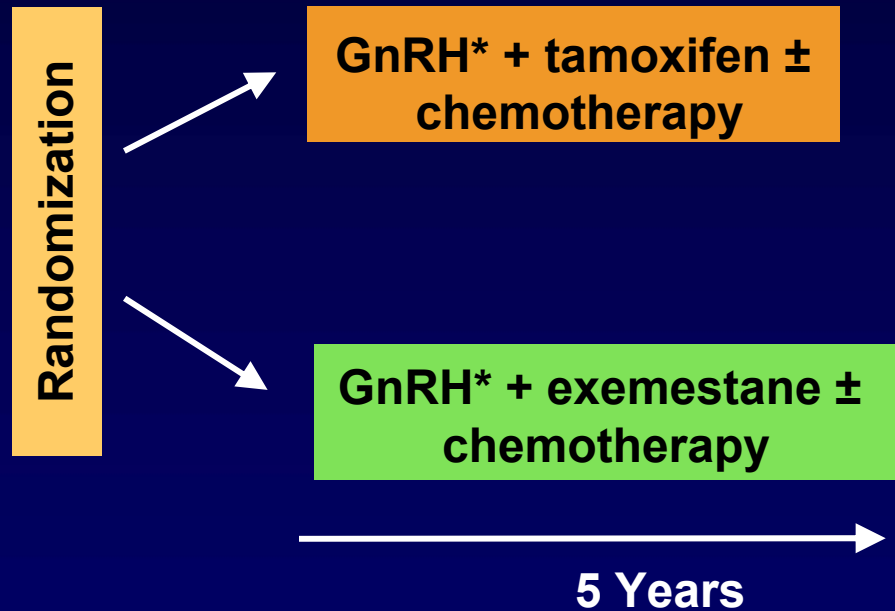
Enrolled as of 06/09: 2061

Eligibility:

Premenopausal

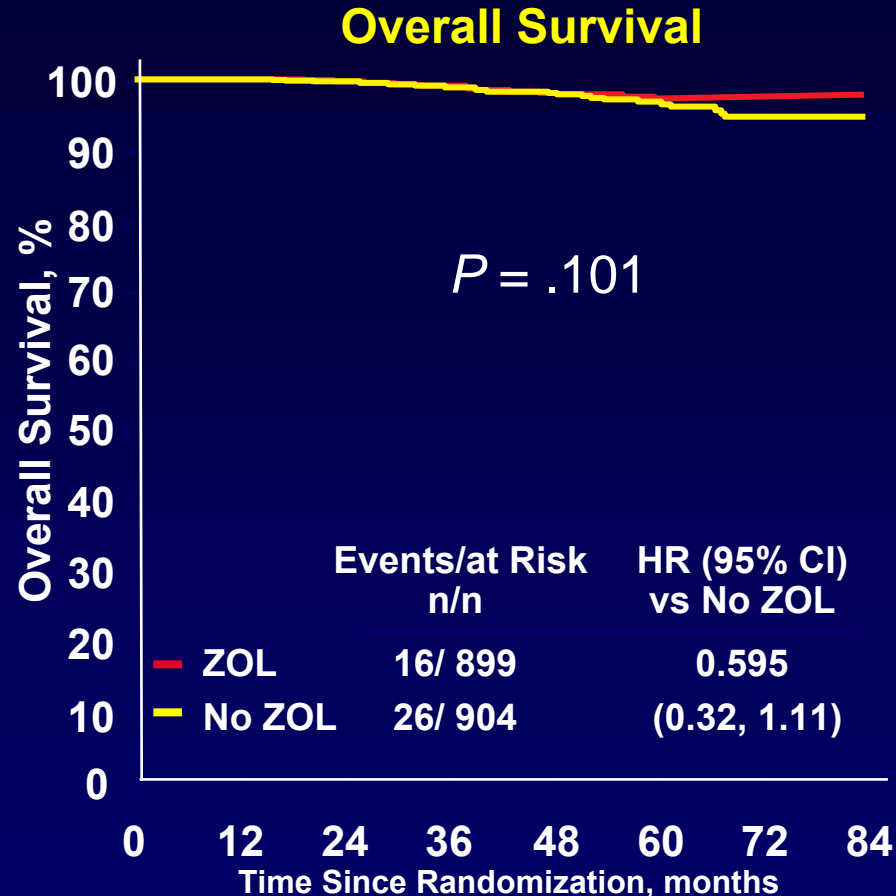
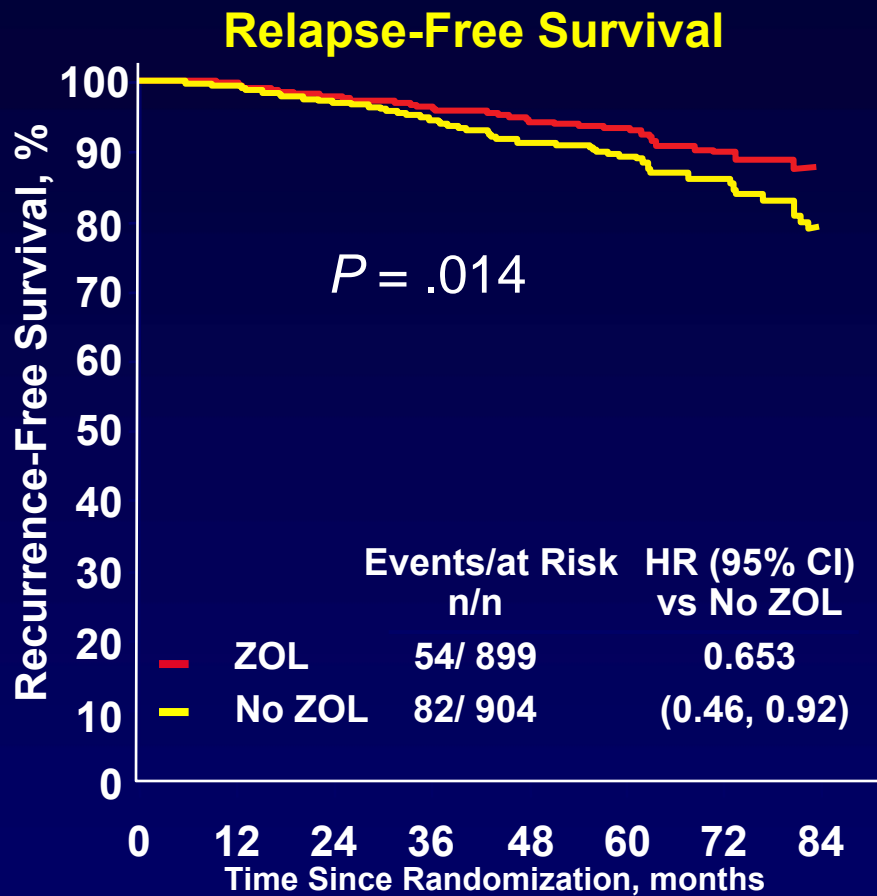
ER  $\geq$  10% and/or PgR  $\geq$  10%

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

	0	12	24	36	48	60	72	84
No ZOL	904	832	714	538	408	241	145	47
ZOL	899	846	730	555	414	257	123	54

	0	12	24	36	48	60	72	84
No ZOL	904	838	735	565	441	265	161	60
ZOL	899	851	744	573	434	270	131	59

# Case #4: My Opinion

- 49-year-old perimenopausal patient (ECOG 0): pT2, pN1 (1/12), G3, Ki 67 20%, ER (60%) and PR (40%) positive, HER2 negative
- CIA for at least two years
- **(Repeat) determination of menopausal status**
  - FSH, LH, Anti Müllerian Hormone (AMH), (E<sub>2</sub>)
- **If perimenopausal hormonal status**
  - Continue TAM
  - Consider AI if definitely postmenopausal
- **If postmenopausal hormonal status**
  - Switch to AI
  - Consider bone health (bone density measurement before endocrine therapy)

# Conclusions

- **Chemotherapy and endocrine treatment has additive benefit**
- **Delayed recovery from chemotherapy induced amenorrhoea may occur**
- **Standard endocrine testing unreliable**
- **If in doubt, stick with tamoxifen**
- **Contribution of OS to chemo + TAM in progress**