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Interdisziplinäres
Brustzentrum München

Case #4 – Choice of Adjuvant Endocrine Therapy for a Perimenopausal Patient

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Case #4

- Forty-seven year old patient, ECOG 0
- Two years ago: Breast right side, pT2 pN1 (2/12) G3
- ER (70%) and PR (40%) positive, HER2 negative
- TREATMENT COURSE:
  - Breast conserving surgery and radiation therapy
  - FEC-100 x 6 cycles with amenorrhea since end of chemotherapy
  - Adjuvant Tamoxifen for now 2 years
- **Clinical Questions:**
  - How to assess menopausal status?
  - When is an amenorrhoic patient considered postmenopausal?
  - Optimal endocrine therapy for perimenopausal situation?

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(Chemo-)Endocrine Treatment in Premenopausal Patients

	Oxford / AGO LoE / GR	
Standard therapy:		
Chemotherapy	1a A	++
Endocrine responsive tumors		
and / or endocrine therapy	1a A	++

Indication for endocrine or chemo-endocrine therapy depends on the individual risk of recurrence

(Chemo-)Endocrine Therapy
of Premenopausal Patients
with Endocrine Responsive Tumors

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Version 2008.1.1

	Oxford LoE / GR		AGO
➢ **High or intermediate risk**			
➢ Chemo → TAM	1a	A	++
➢ Chemo → TAM + GnRHa	1b	B	+/-*
➢ <40 yrs	2a	C	+*
➢ **Low or intermediate risk**			
➢ TAM alone	1a	A	++
➢ TAM + GnRHa	1b	B	+*
➢ GnRHa alone	1b	B	+/-

* Study participation recommended

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Tamoxifen Efficacy Does Not Differ Significantly According to Patient Age

Table 1. Five Years of Tamoxifen in ER-Positive or ER-Unknown Breast Cancer by Age: Early Breast Cancer Trialists' Collaborative Group Overview Analysis

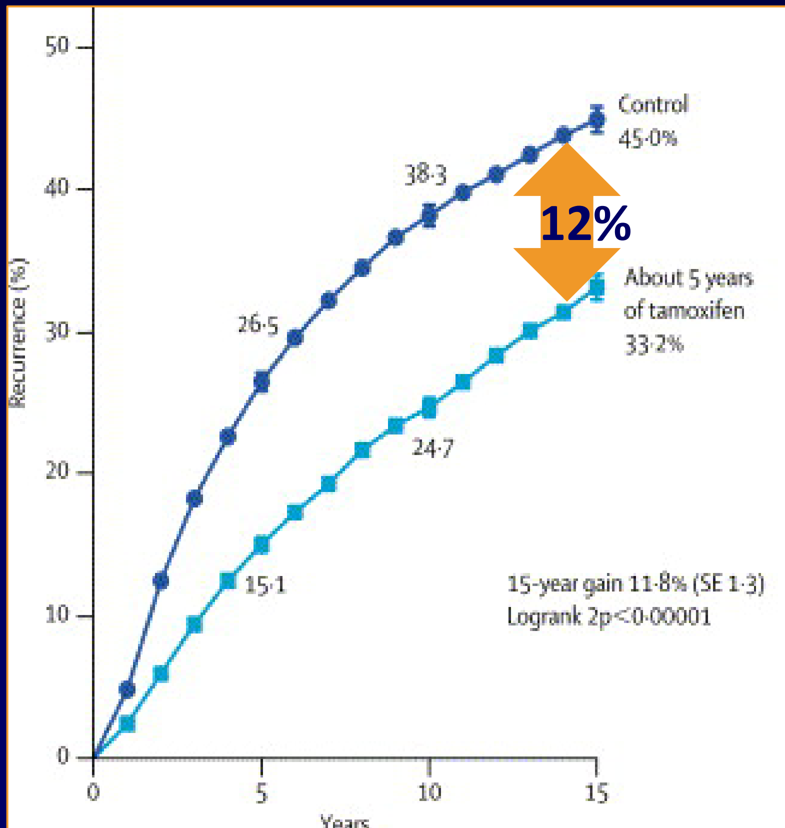
	Annual Risk Ratio ± SE			
	Breast Cancer Recurrence Rate		Breast Cancer Death Rate	
	Risk Ratio	SE	Risk Ratio	SE
For all age groups	0.59	0.03	0.66	0.04
Age, years				
< 40	0.56	0.10	0.61	0.12
40-49	0.71	0.07	0.76	0.09
50-59	0.66	0.05	0.76	0.07
60-69	0.55	0.05	0.65	0.06
≥ 70	0.49	0.12	0.63	0.15

NOTE. Reproduced with permission.[7]
Abbreviation: ER, estrogen receptor.

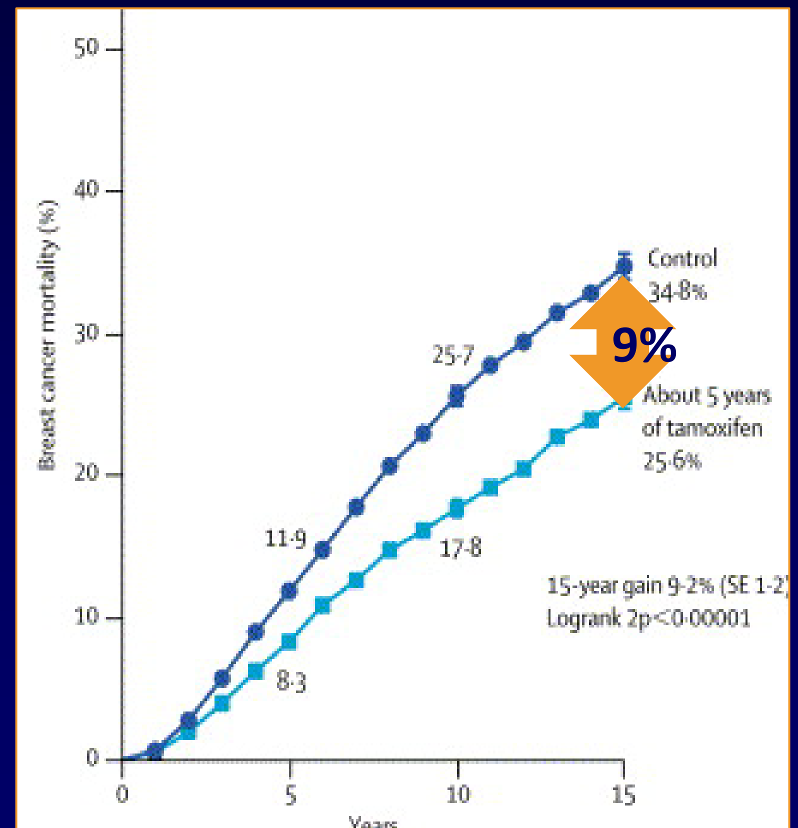
Parton M & Smith I. *J Clin Oncol* 2008; 26: 745-752 after EBCTG, *Lancet* 2005

EBCTCG – Tamoxifen

Recurrence



Breast Cancer Mortality



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EBCTCG Group. *Lancet* 2005; 365:1687-717

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?

Tamoxifen

AI

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

↑ Arthralgia/myalgia
↑ Osteoporosis risk

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Rates of Chemotherapy Induced Amenorrhea

Agents	"younger" women (≤ 40y)	"older" women (> 40y)
Alkalyting	18 - 61 %	61 – 97 %
Anthracyclines	~ 32 %	~ 88 %
Taxanes (+A)	~ 61%	~ 84%

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Walshe JM et al. *J Clin Oncol.* 2006; 24: 5769-5779

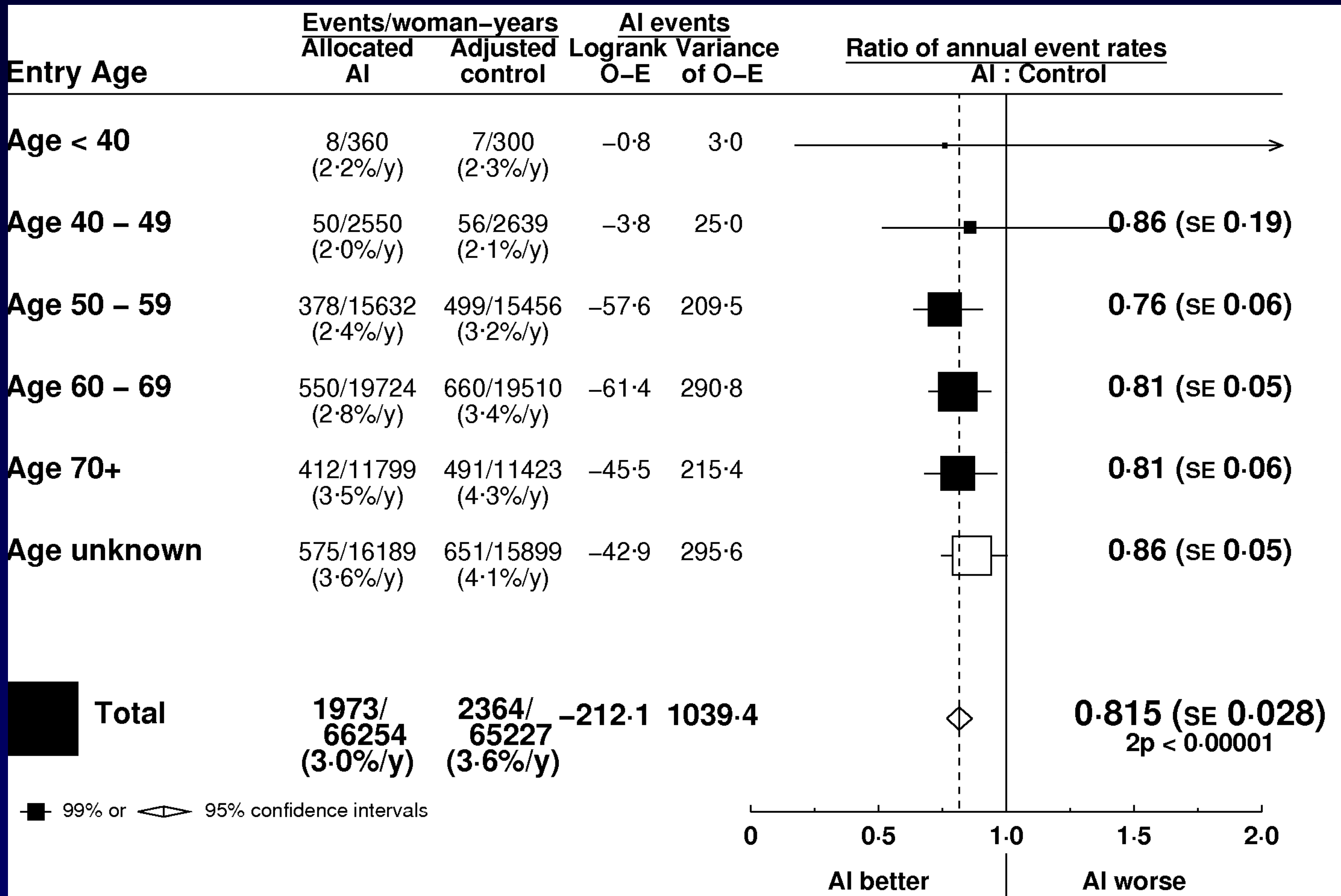
Predictors for Early Relapse AI vs Tam (BIG 1-98)

• node positivity*	$P < 0.001$
• ER and PR neg	$P < 0.001$
• G 3	$P < 0.001$
• HER-2 +	$P < 0.001$
• large tumor size*	$P = 0.001$
• treatment with tamoxifen	$P = 0.002$
• vascular invasion*	$P = 0.02$

* tendency for higher efficacy with Letrozole

Mauriac L et al. *Ann Oncol* 2007; 18(5):859-867

2006 Overview: Adjuvant Aromatase Inhibitors Effects on Recurrence By Age



No statistically significant efficacy difference by age.

Case #4: AI in Infertility Treatment

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(3):825–833
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doi: 10.1210/jc.2006-1673

Follicular Phase Dynamics with Combined Aromatase Inhibitor and Follicle Stimulating Hormone Treatment

Mohamed A. Bedaiwy, Noha A. Mousa, Navid Esfandiari, Rachel Forman, and Robert F. Casper

Reproductive Sciences Division, Department of Obstetrics and

3000

Letrozole and FSH

Human Reproduction Vol.18, No.8 pp.1588–1597, 2003

DOI: 10.1093/humrep/deg311

Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulation in women with unexplained infertility

M.F.M.Mitwally[1,2,3] and R.F.Casper[1,4]

Use of AIs in Perimenopause: Royal Marsden Experience

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

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

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

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Biochemical Monitoring of Ovarian Function in Perimenopause

- Single measurement of FSH, (LH), E_2, beta inhibin reflects function only at that time point, but is not predictive
- Tests used for E_2 measurements are highly unreliable in perimenopause, as they do not extract or purify E_2 from plasma
- Measurement in patients receiving a steroidal AI cross-react even with most specialized immunoassays

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

Use of AIs in Perimenopause

- No use under age of 40 yrs
- For patients age > 40 yrs and no biochemical monitoring is favored or available
  - Tamoxifen
  - GnRH + Tamoxifen
  - (GnRH + AI)
  - Ovarian Ablation + AI

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

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If Use of AIs is Considered in Perimenopause (< 55 yrs)

- Serial monthly measurement of FSH and E_2
  - For at least 6 months
  - For AI after Tam situation even longer
- If E_2 remains > 10 pmol/l = AI is not fully effective
  - Switch back to Tam
  - 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

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

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(Chemo-)Endocrine Therapy
of Premenopausal Patients
with Endocrine Responsive Tumors

	Oxford LoE	/ GR	AGO
GnRH + AI	5	D	+/-*
AI alone	1c	A	- -
AI after GnRHa (induced amenorrhea)	5	D	- -
Upfront AI in patients with chemotherapy-induced amenorrhea	4	C	- -

* Study participation recommended

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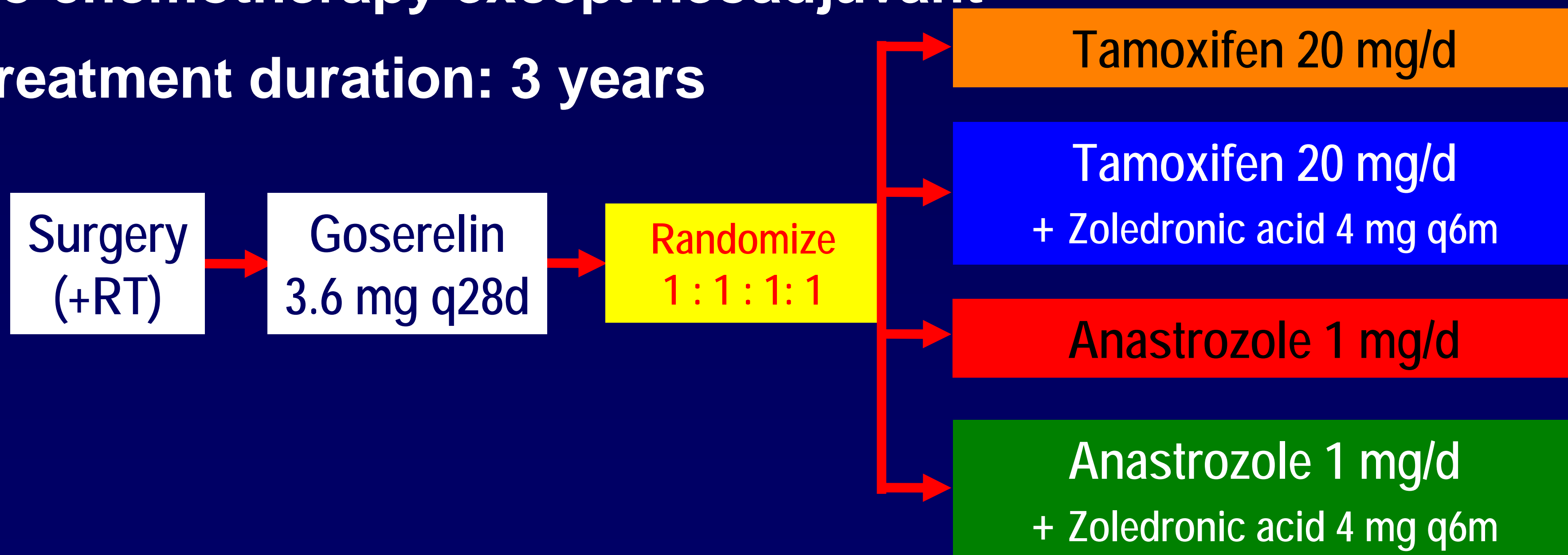
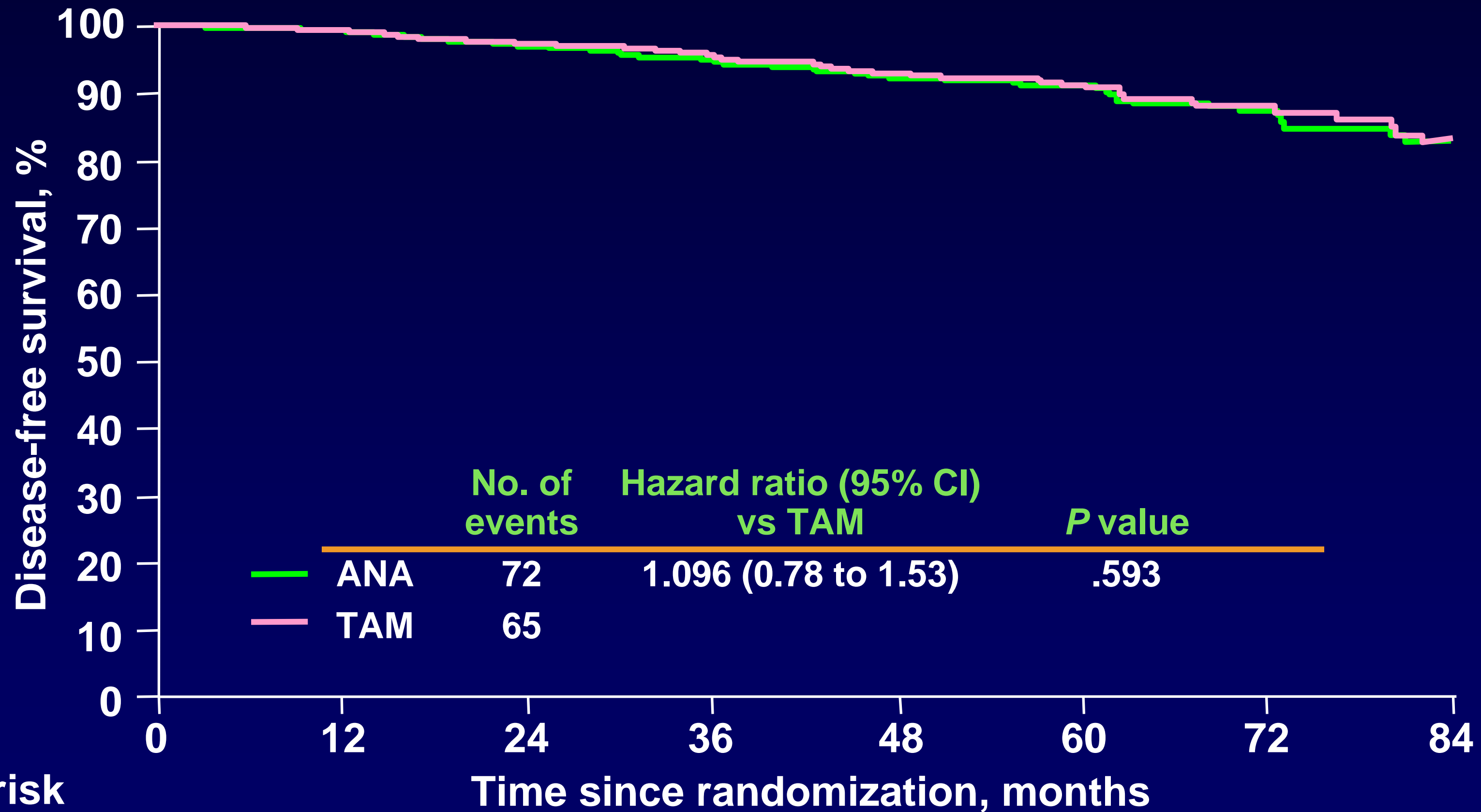
Trial ABCSG-12: AIs in Premenopausal Patients/ does zoledronic acid improve patients' outcome?

- Accrual 1999-2006
- 1,803 premenopausal breast cancer patients
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



Gnant M, et al. Presented at: ASCO 2008, Chicago, IL. Abstract LBA4.

Primary End Point: Disease-Free Survival
No Significant Difference Between TAM and ANA



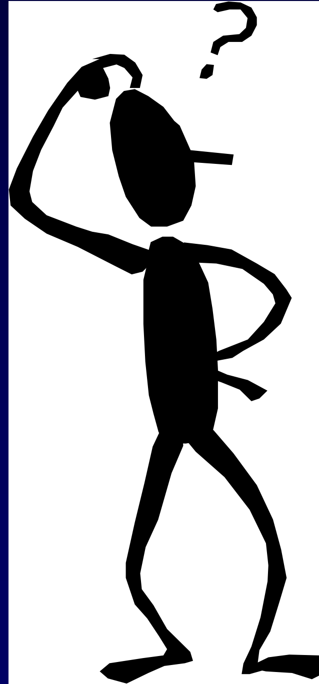
No. at risk

	0	12	24	36	48	60	72	84
TAM	900	834	718	552	411	243	129	50
ANA	903	844	725	540	411	255	139	51

Median follow-up = 48 months.

Update of Gnant M, et al. Presented at: ASCO 2008. Chicago, IL. Abstract LBA4.

Case #4: How to determine menopausal status ?



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Adjuvant Endocrine Therapy in Premenopausal Patients

Assessment of menopausal status:

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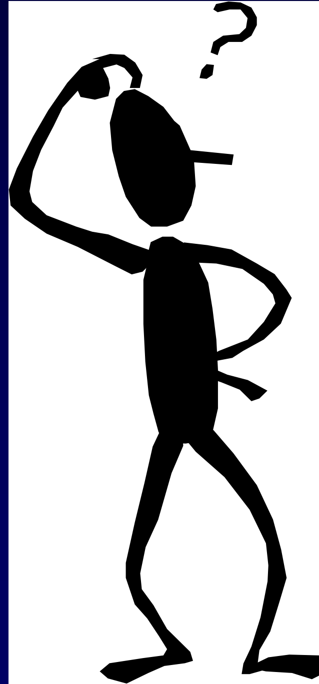
➢ Menstruation history	+
➢ FSH, E2	++

Case #4: How about an AI at a later stage ?



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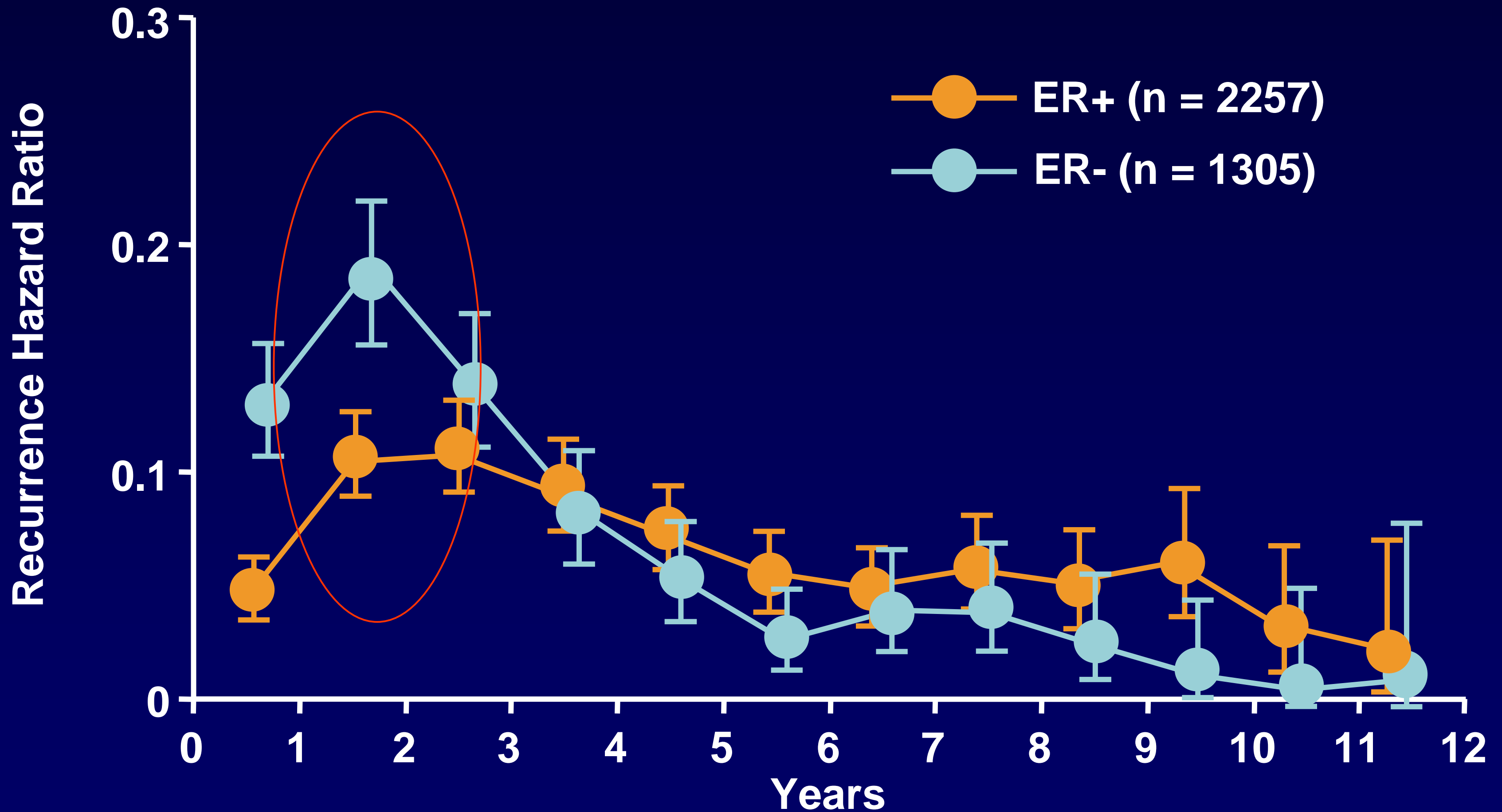
Long-term Risk of Breast Cancer Recurrence According to ER Status



Saphner T et al. *J Clin Oncol* 1996;14:2738-2746.

Adjuvant Aromatase Inhibitors in **postmenopausal** patients: **Replacing 5 Years of Tamoxifen as the Gold Standard**

Three Strategies

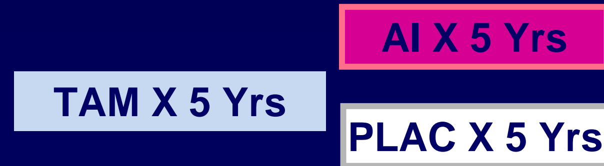
AIs as

Letrozole

AIs After 2-3 Yrs of TAM

Anastrozole
Exemestane

AIs After 5 Years of TAM



Letrozole
Anastrozole
Exemestane

Is Exemestane Consistant Across Subgroups for Disease-Free Survival ?

Favors Exemestane

Favors Tamoxifen

Subgroup	HR (95% CI)
Nodes –ve (2384)	0.74 (0.58, 0.95)
Nodes +ve (2038)	0.71 (0.59, 0.84)
No previous CT (3103)	0.74 (0.62, 0.89)
Previous CT (1499)	0.76 (0.61, 0.95)
ER +ve (4042)	0.75 (0.64, 0.87)
ER Unknown (560)	0.79 (0.55, 1.14)
Prior Tam <=2.5 yrs (2764)	0.76 (0.63, 0.92)
Prior Tam >2.5 yrs (1838)	0.74 (0.60, 0.92)
Age <60 yrs (1480)	0.79 (0.61, 1.03)
Age 60-69 yrs (1969)	0.68 (0.54, 0.85)
Age 70+ yrs (1153)	0.83 (0.64, 1.07)
DFS (Adjusted)*	**0.74 (0.64, 0.85)** P<0.0001

0.5 0.6 0.8 1.0 1.2

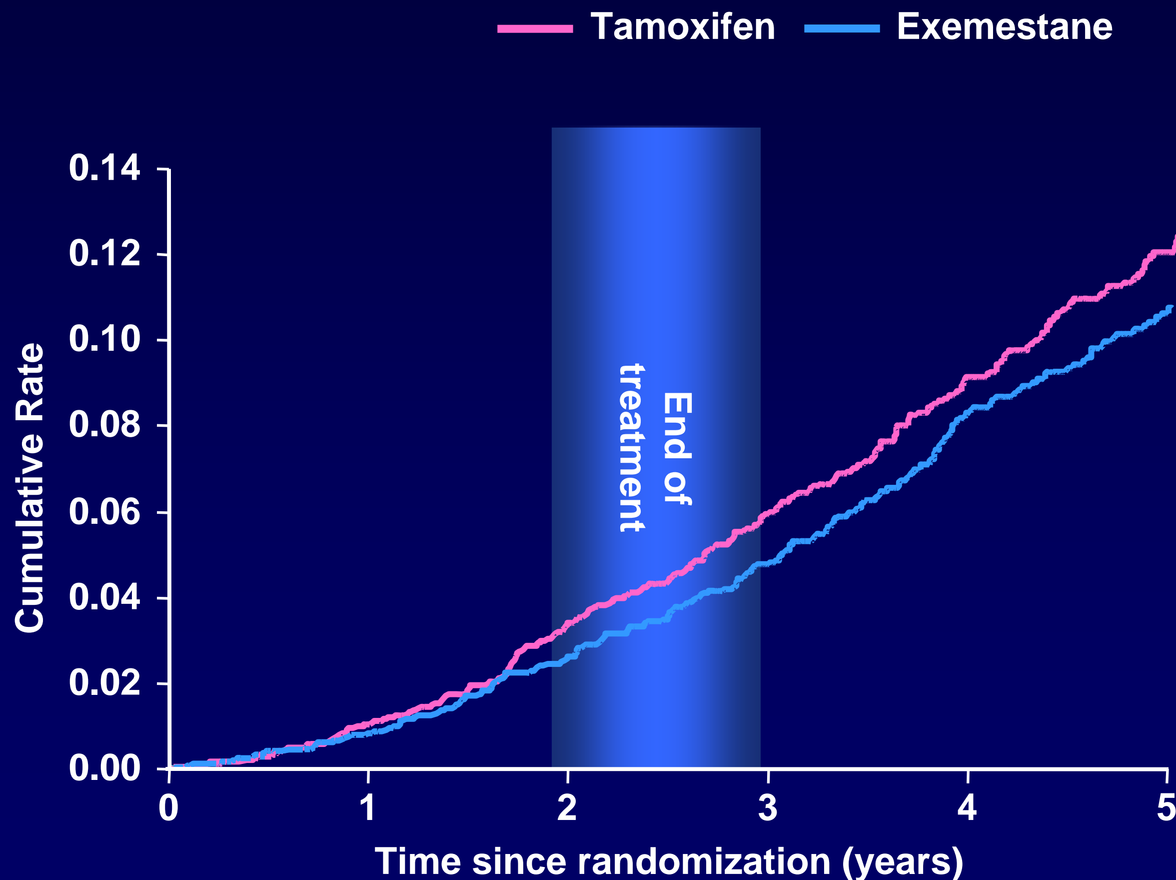
Hazard ratio (95% CI)

* Adjusted for Nodal Status, Chemotherapy Use & HRT Use

Coombes RC et al. *Lancet* 2007; 369: 559-70.

Cumulative HR – Overall Survival

ER+/Unknown : 17% reduction in the risk of mortality



251 vs 210 events in favour of exemestane [HR=0.83, 95% CI/0.69-0.99 p=0,04]

Coombes RC et al. *Lancet* 2007; 369: 559-70.

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Endocrine Therapy after 5 Years of Tamoxifen

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Letrozole 5 yrs	1b	A	+
➢ node-positive disease	1b	B	++
➢ long tamoxifen-free interval (up to 30 months)	4	D	+
Anastrozole 3 yrs	2b	B	+
Exemestane 5 yrs	2b[a]	B	+
Tam > 5 yrs	2b[a]	C	+

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Case #4: My opinion

- 47 year old perimenopausal patient (ECOG 0): pT2, pN1 (2/12), G3, ER (70%) and PR (40%) positive, HER2 negative
- CIA for at least two years
- (Repeat) determination of menopausal status
  - FSH, LH, E_2
- If perimenopausal hormonal status
  - Continue TAM
  - Consider AI (EAT) if surely postmenopausal
- If postmenopausal hormonal status
  - Switch to AI
  - Consider bone health (bone density measurement before endocrine therapy)

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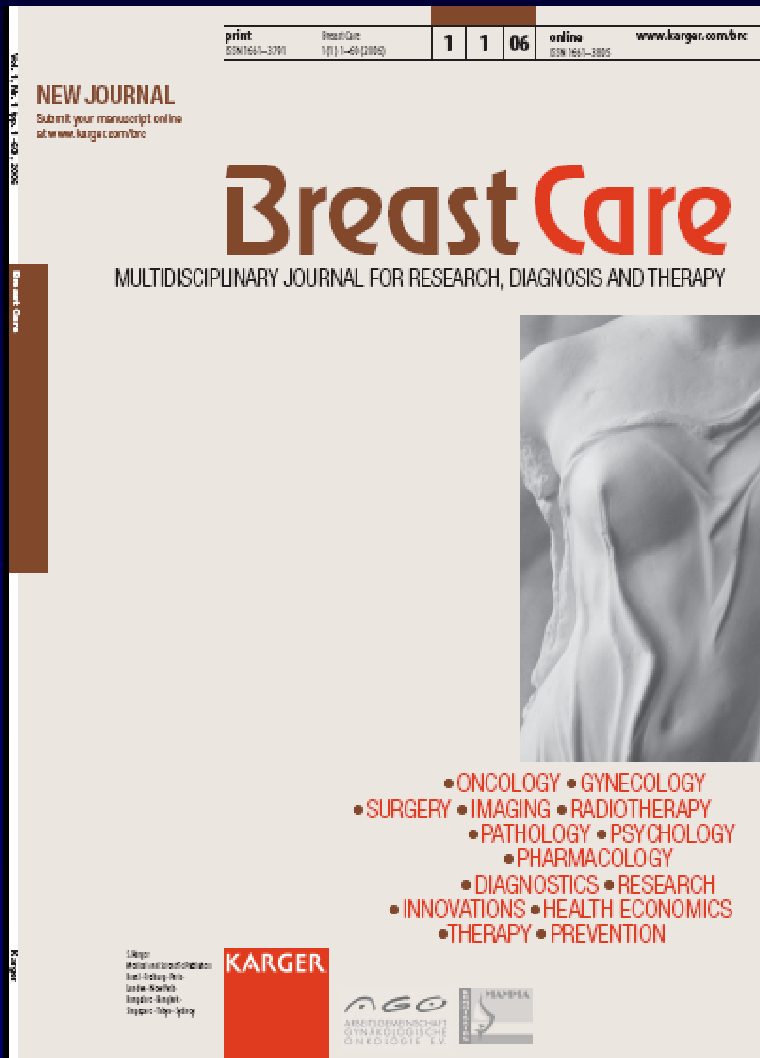
Evidence-based Breast Cancer Therapy



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