

Case #1 – Choice of Adjuvant Endocrine Therapy for a Postmenopausal Patient at Intermediate Risk of Recurrence



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Case #1

- **60 year old postmenopausal patient (ECOG 0): pT1c, pN0 (sn), G2, ER (70%) and PR (40%) positive, HER2 negative**
- **Clinical Questions:**
 - Risk for relapse ?
 - Is there a relevant additional benefit from adjuvant chemotherapy ?
 - Optimal endocrine therapy ?



St. Gallen 2007: Risk Categories and Therapy Recommendations for Primary Breast Cancer

Risk category and therapy recommendation (endocrine responsive)

Intermediate Risk



Node negative + at least one of the properties below:

pT > 2 cm or Grade 2–3 or peritumoral vascular invasion
or HER2/neu overexpression or age < 35 years

Node positive (1 - 3 LK) without HER2/neu overexpression

Chemotherapy → endocrine therapy

or

Endocrine therapy alone (various options)

Trastuzumab + Chemotherapy if HER2 positive

Case #1: Adjuvant Online estimates

Adjuvant! for Breast Cancer (Version 8.0)

Patient Information

Age:

Comorbidity:

ER Status:

Tumor Grade:

Tumor Size:

Positive Nodes:

Calculate For:

10 Year Risk:

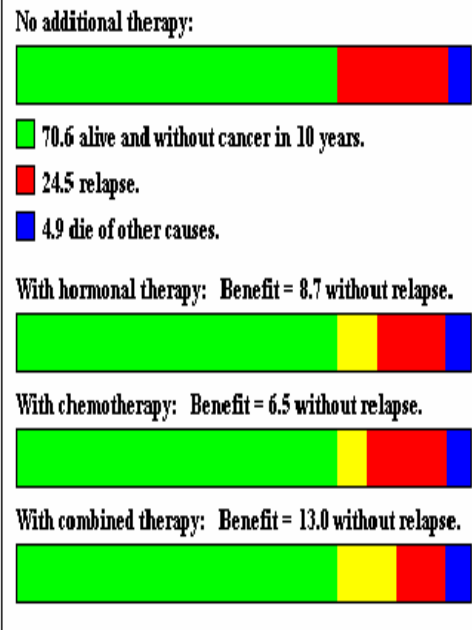
Adjuvant Therapy Effectiveness

Horm:

Chemo:

Hormonal Therapy:

Chemotherapy:



Adjuvant! for Breast Cancer (Version 8.0)

Patient Information

Age:

Comorbidity:

ER Status:

Tumor Grade:

Tumor Size:

Positive Nodes:

Calculate For:

10 Year Risk:

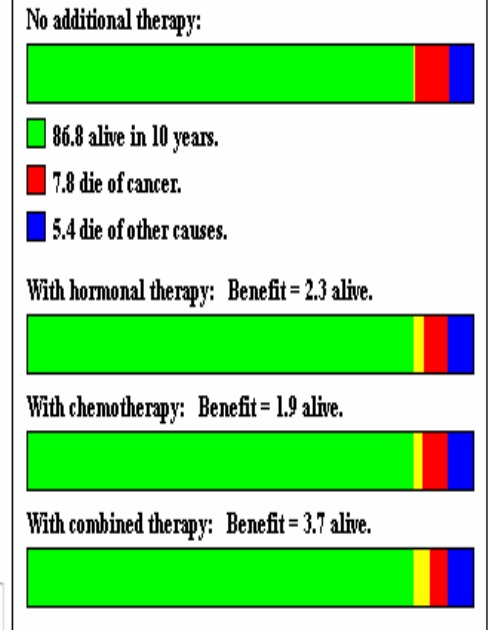
Adjuvant Therapy Effectiveness

Horm:

Chemo:

Hormonal Therapy:

Chemotherapy:



Case #1: Additional Risk Assessment



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Summary	Not Recommended	Recommended
P53	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Cathepsin D	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
uPA and PAI-1	Screening, diagnosis, staging, surveillance, or monitoring.	To determine prognosis. For treatment planning. To guide use of CMF-based adjuvant chemotherapy.
Cyclin E Fragments	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Proteomic Analysis	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Multiparameter Gene Expression Analysis	Screening, diagnosis, staging, surveillance, or monitoring. Not for prediction of hormonal therapies other than tamoxifen or other chemotherapy regimens.	Oncotype™ for prognosis for patients with node-negative, ER positive breast cancer who will receive tamoxifen. Guiding use of adjuvant tamoxifen and adjuvant chemotherapy (specifically CMF).
Multiparameter Gene Expression Analysis, other	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Bone Marrow Micrometastases	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Circulating tumor cell assays	Screening, diagnosis, staging, prognosis, surveillance, predicting or monitoring.	



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Prognostic Factors in Node-negative Breast Cancer

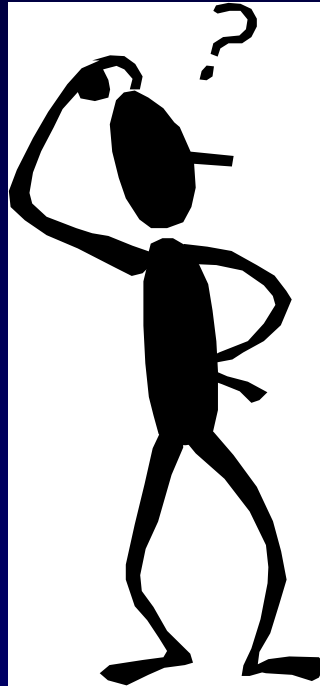
**Oxford / AGO
LoE / GR**

Factor

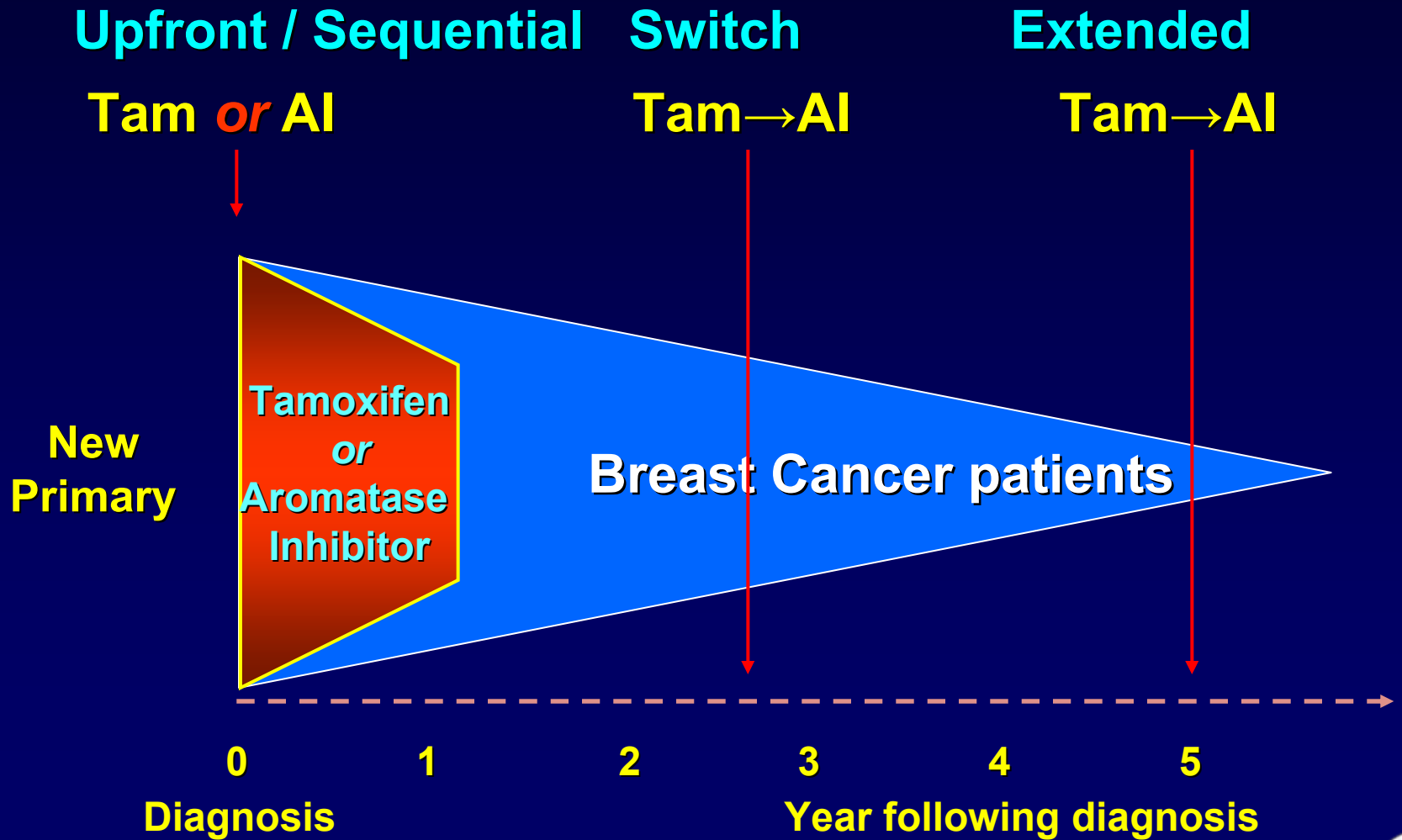
➤ Grade	2b B ++
➤ Tumor size	2b B +
➤ Age	2b B +
➤ uPA / PAI-1 (ELISA)	1a A +*
➤ Proliferation (SPF, TLI, Ki-67)	2b B +/-
➤ Oncotype DX™	2b B -*
➤ Mammaprint™	2b B -*

*study participation recommended

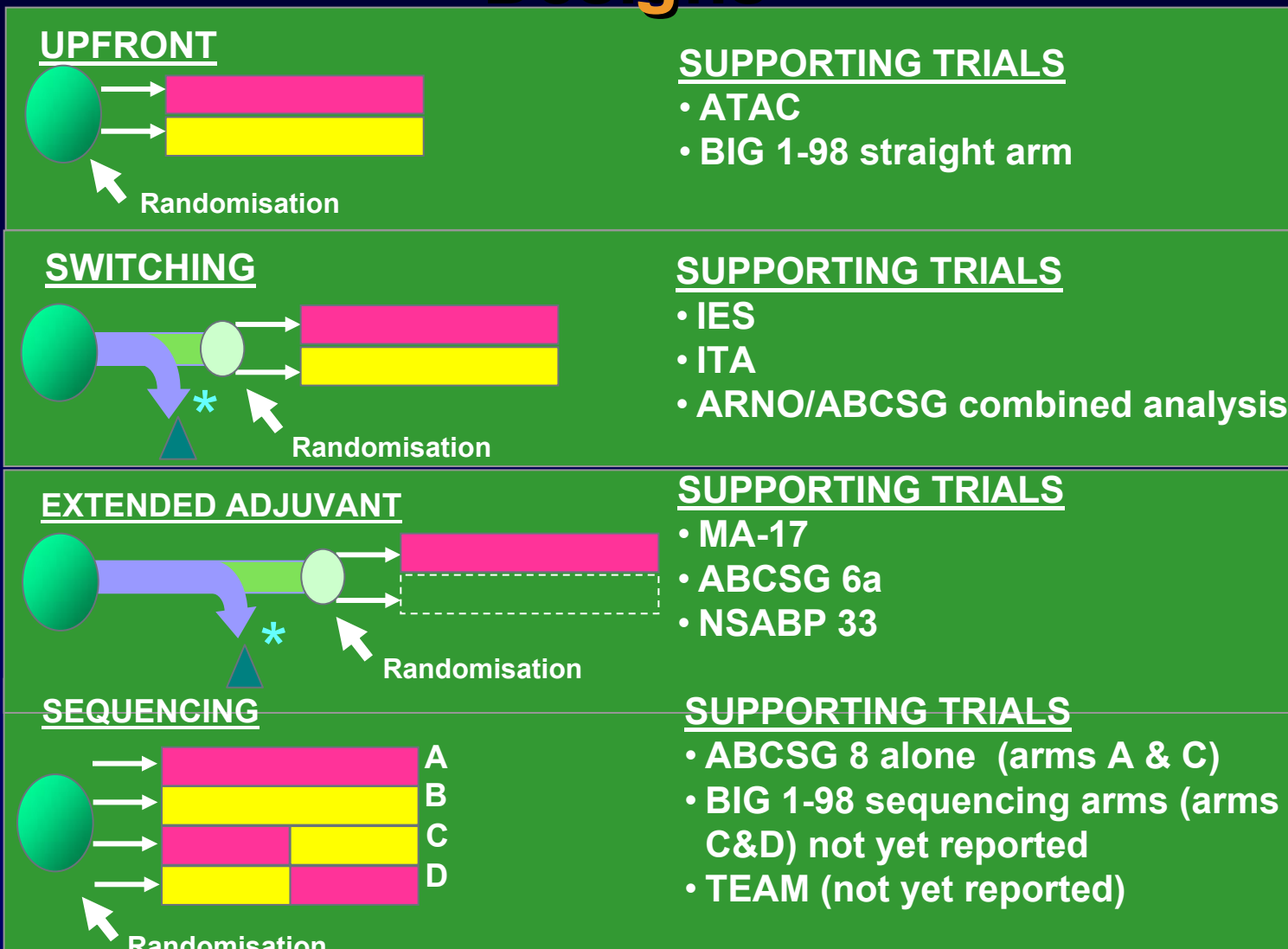
Case #1 - Optimal Endocrine Therapy: Upfront AI or TAM?



Breast Cancer – Treatment Strategy

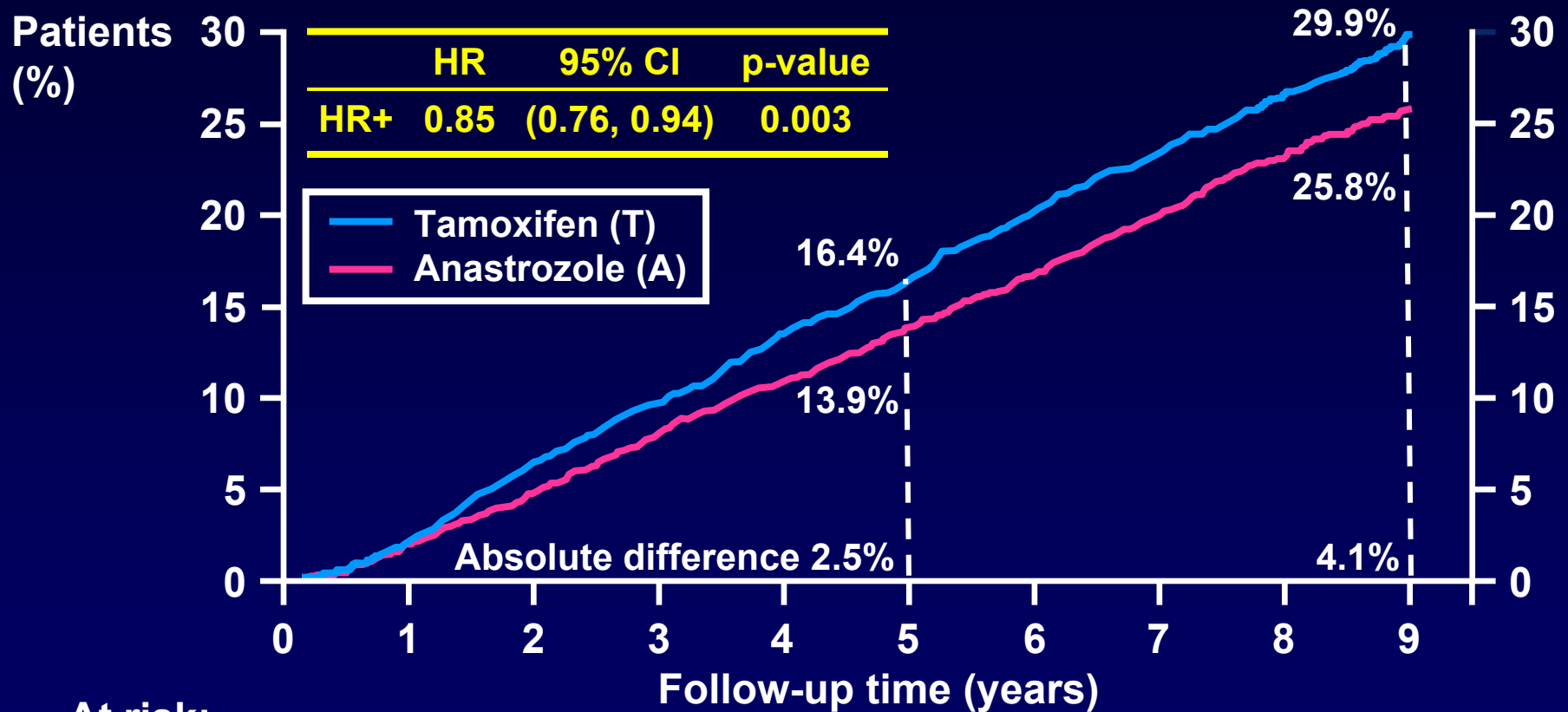


Adjuvant Endocrine Therapy: Trial Designs



* Note that some patients from the original newly diagnosed population are lost due to recurrence or adverse events prior to randomisation.

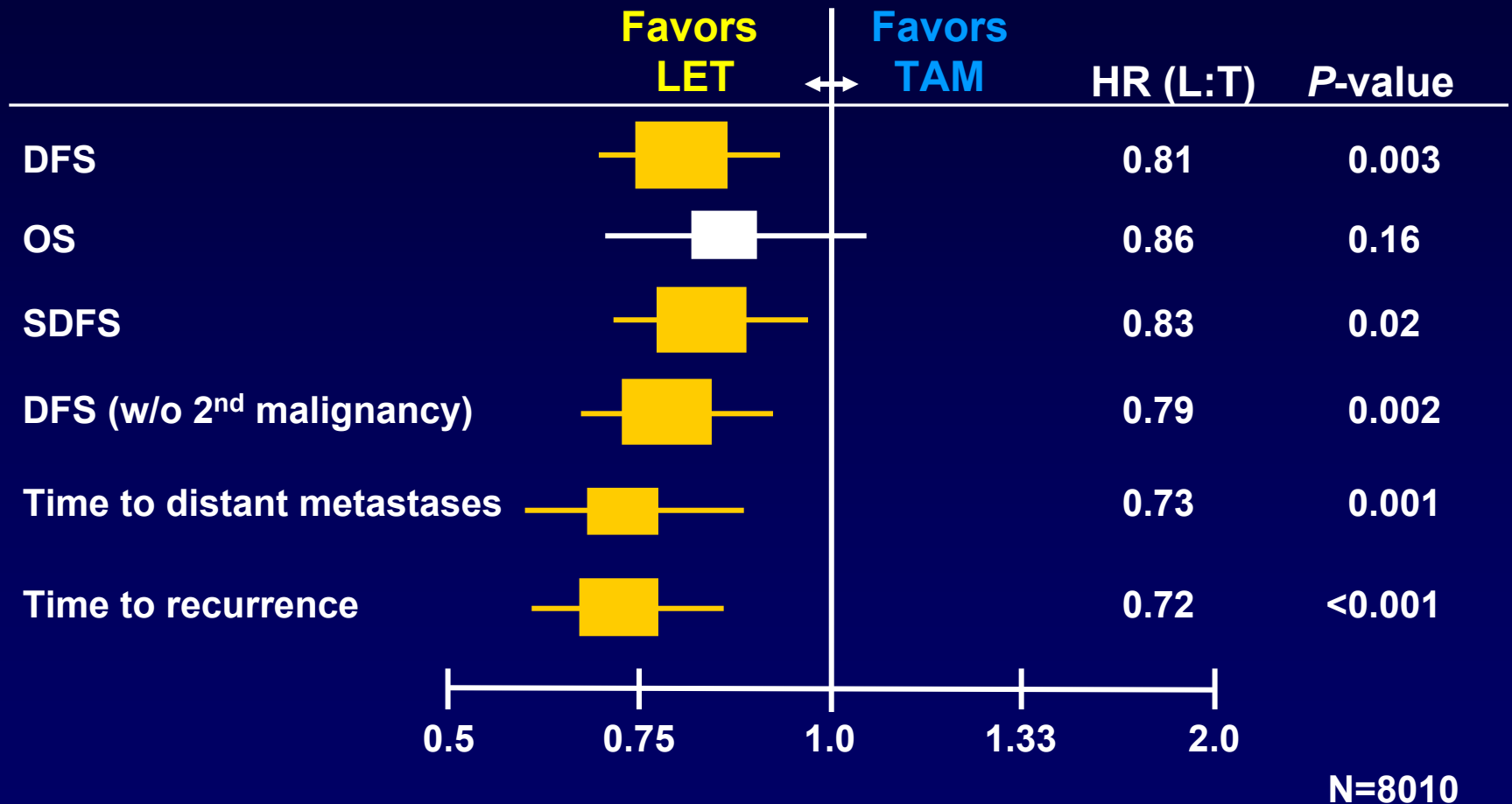
ATAC: Disease-Free Survival (HR+ Patients) 100 Month Median Follow-up



At risk:

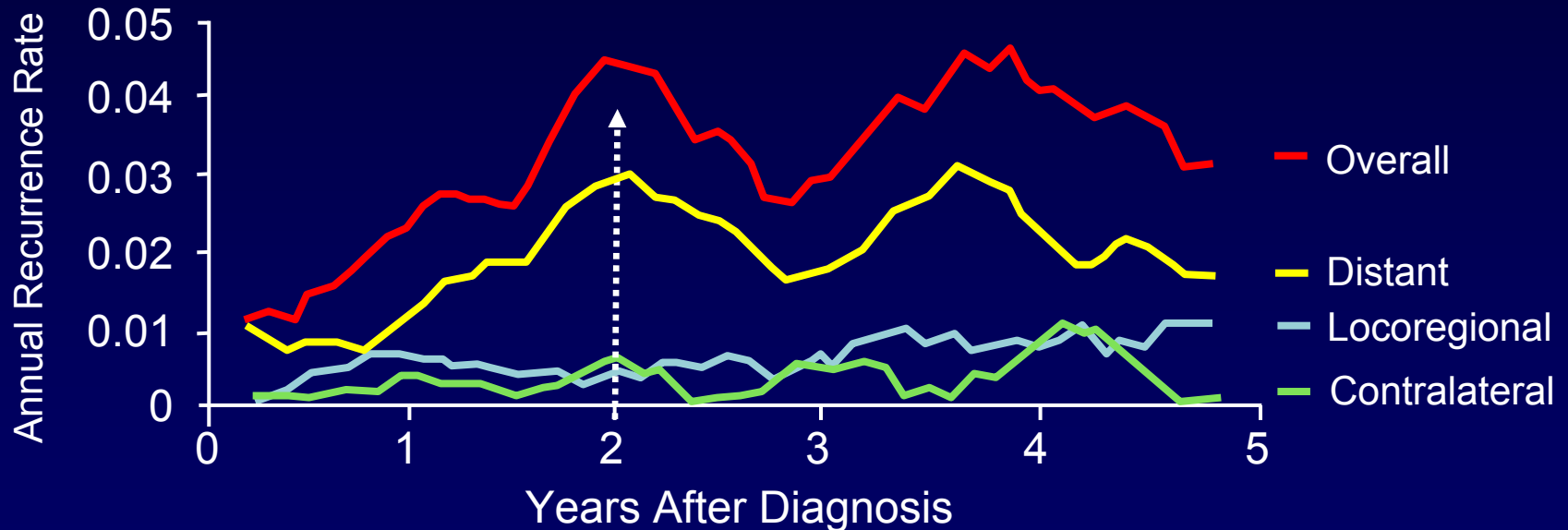
A	2618	2541	2453	2361	2278	2159	1995	1801	1492	608
T	2598	2516	2400	2306	2196	2075	1896	1711	1396	547

BIG 1-98 Efficacy Endpoints: 26 Month Median Follow-up



Distant Metastases Comprise the Majority of Early Recurrences

4245 postmenopausal women with ER+ operable breast cancer, all treated with TAM *

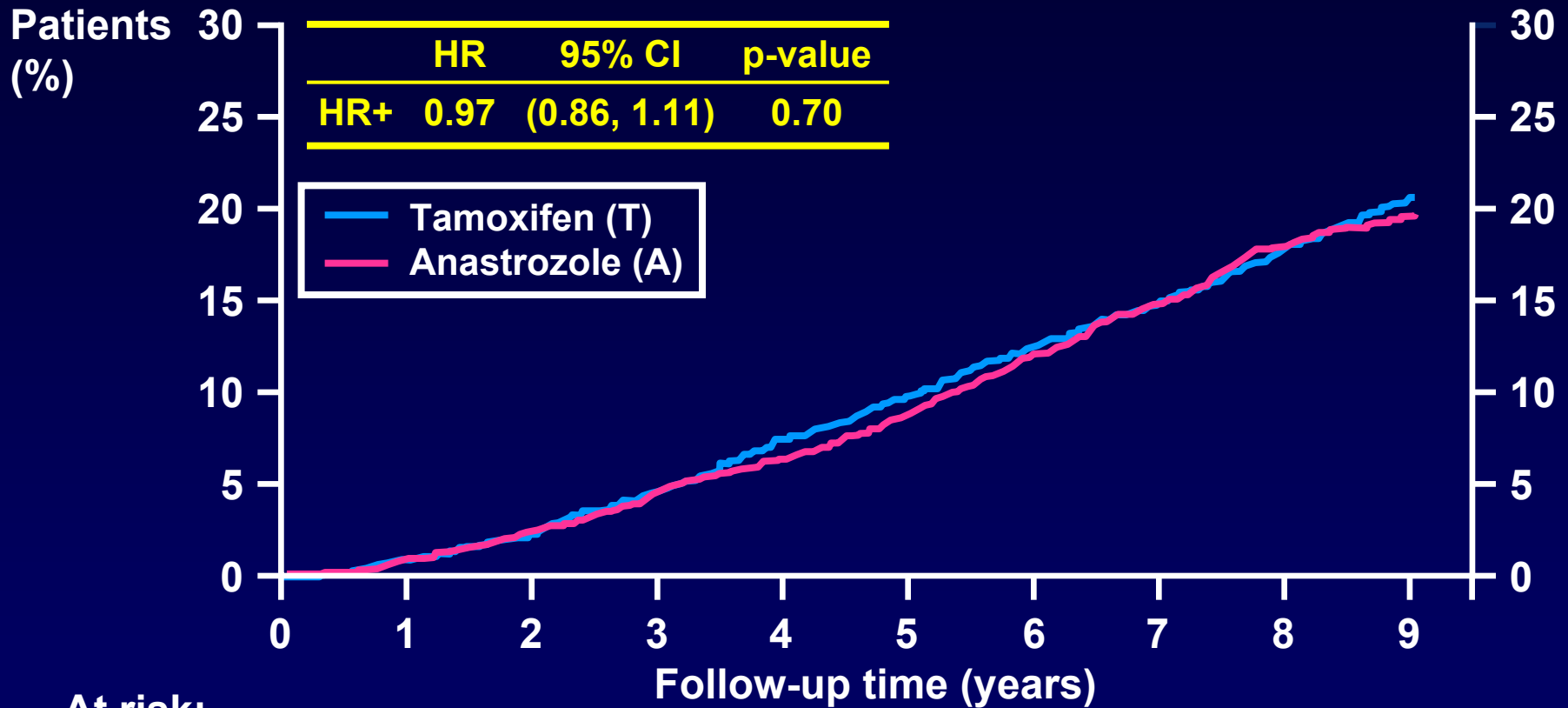


- **Recurrence peak seen at 2 years with tamoxifen treatment**
- **Distant recurrences** are responsible for the initial peak of recurrences seen at 2 years
- Age, tumor size, grade, nodal status, lymphovascular invasion were **predictors of early recurrence** ($P < 0.01$)**

*Doughty et al. *Breast Cancer Res Treat* 2007;106(S1):S145. Abstract 3057.

**Mansell et al. SABCS 2006, Abstract 2091.

Death: All Causes (HR+ Patients) 100 Month Median Follow-up

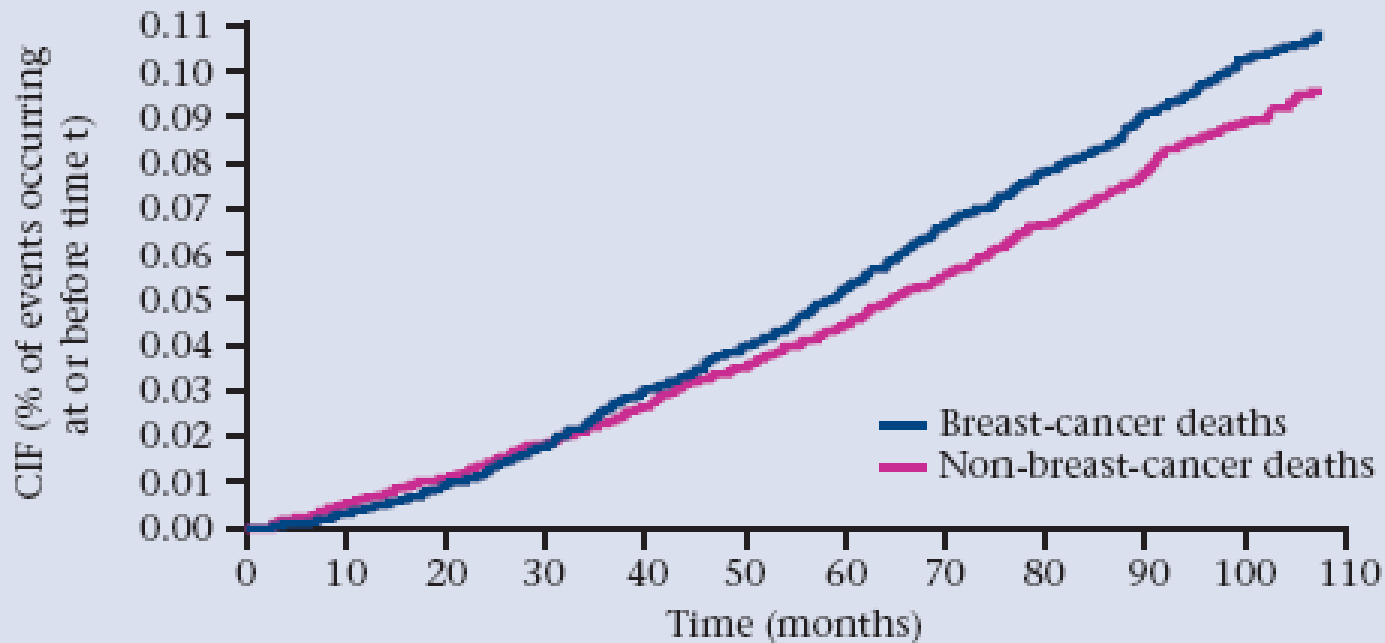


At risk:

A	2618	2567	2511	2445	2389	2274	2102	1911	1586	659
T	2598	2549	2504	2432	2339	2227	2068	1888	1551	620

Upfront AI and Overall Survival: ATAC100 – BC vs. non-BC deaths

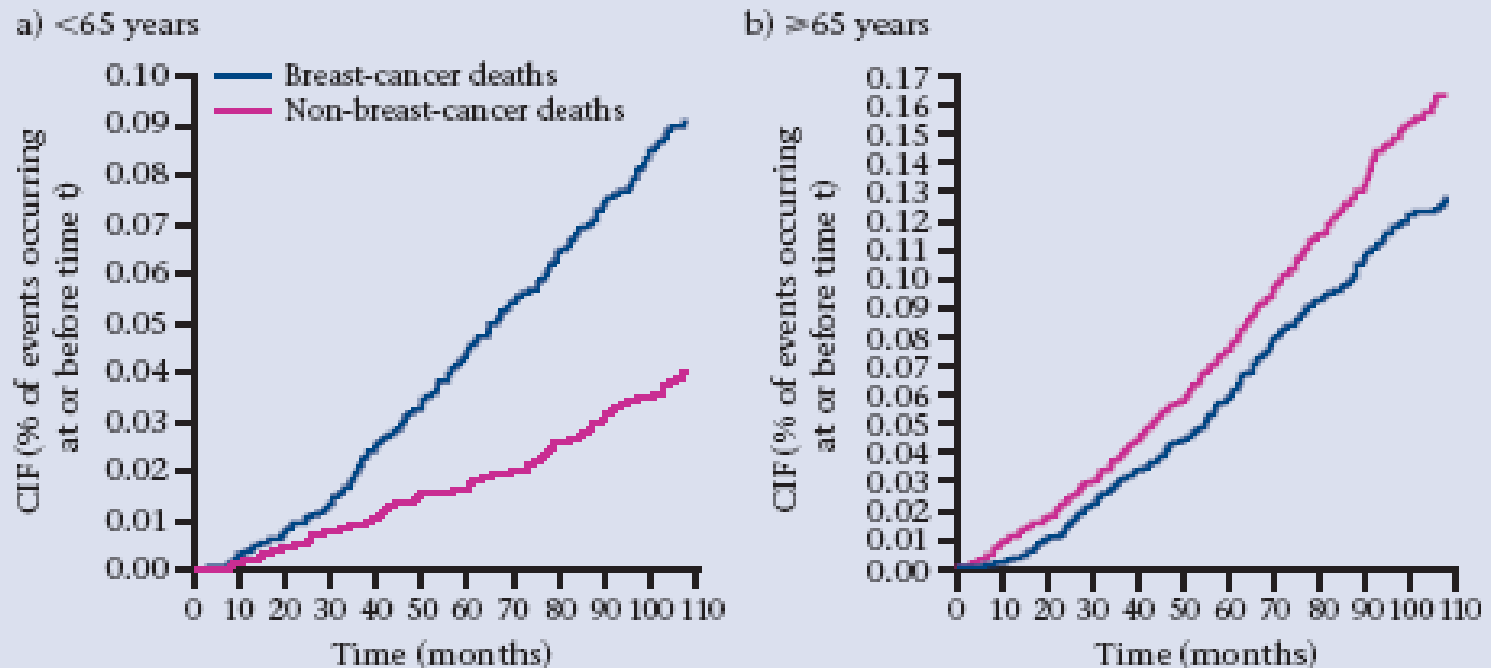
Figure 1. Proportion of deaths without recurrence vs following a recurrence (anastrozole and tamoxifen arms combined) by follow-up time.



CIF, Cumulative Incidence Function

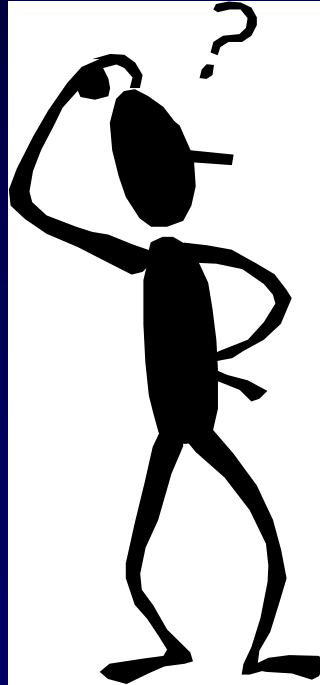
Upfront AI and Overall Survival: ATAC100 – BC vs. non-BC deaths

Figure 3. Effect of age on the proportion of deaths without recurrence and following recurrence (anastrozole and tamoxifen arms combined) by follow-up time.



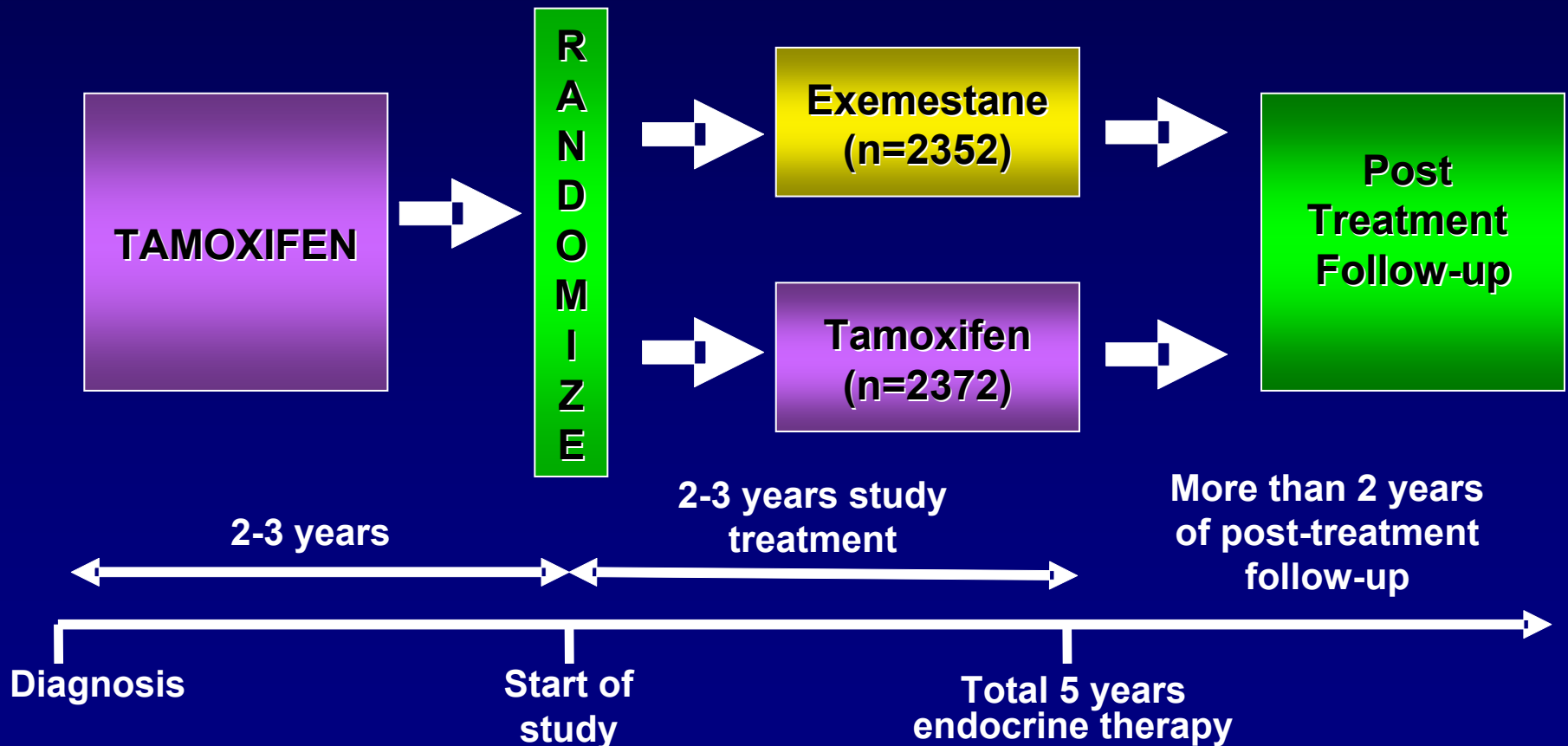
CIF, Cumulative Incidence Function

Case #1 - Optimal endocrine therapy: To switch or not to switch ?

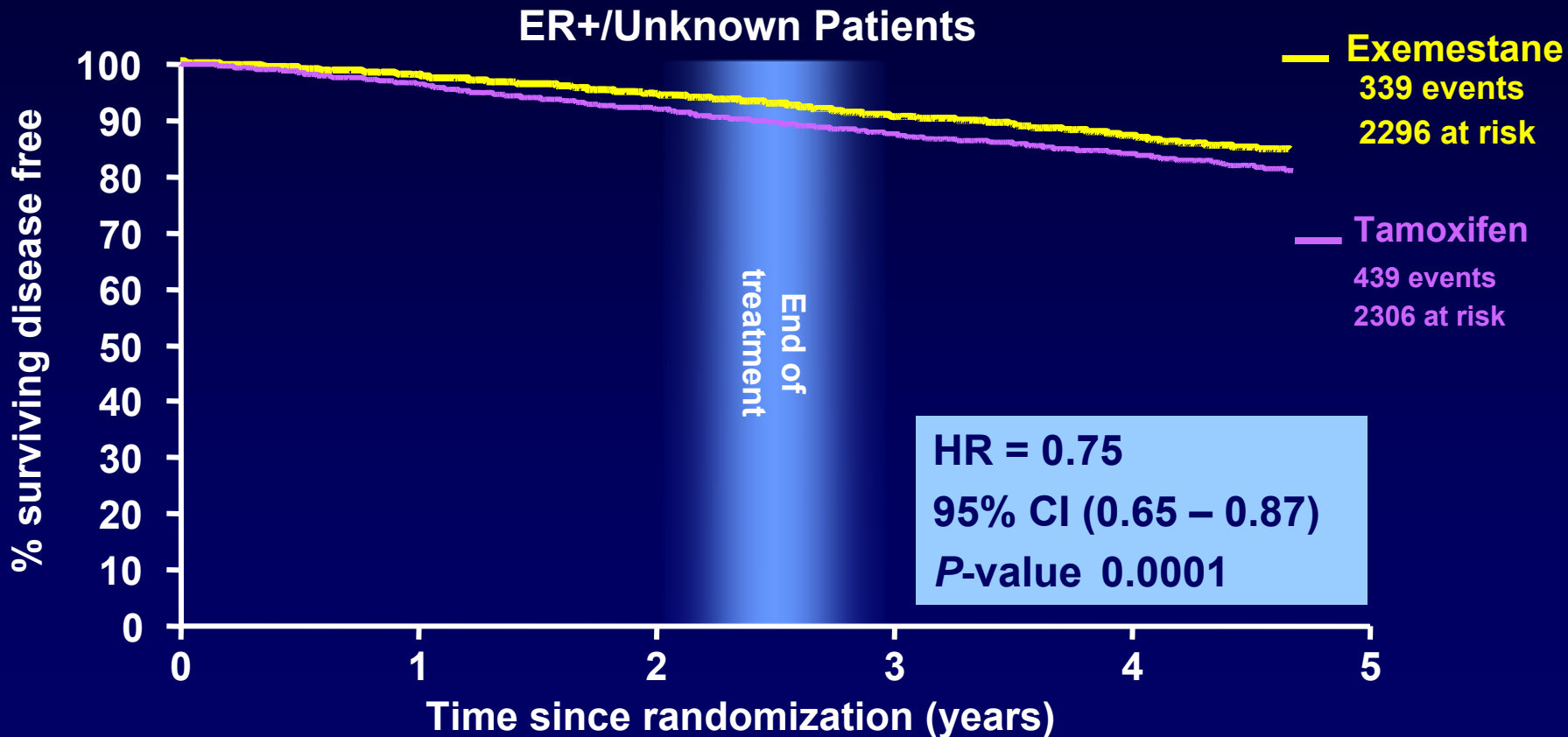


IES Trial Design

- 56 months median follow-up
- Over 99% of patients have completed treatment



Does Exemestane Improve Disease Free Survival?



% absolute difference (95% CI)

2.5 years
3.4 (1.8 – 5.1)

5 years
3.5 (0.1 – 6.9)



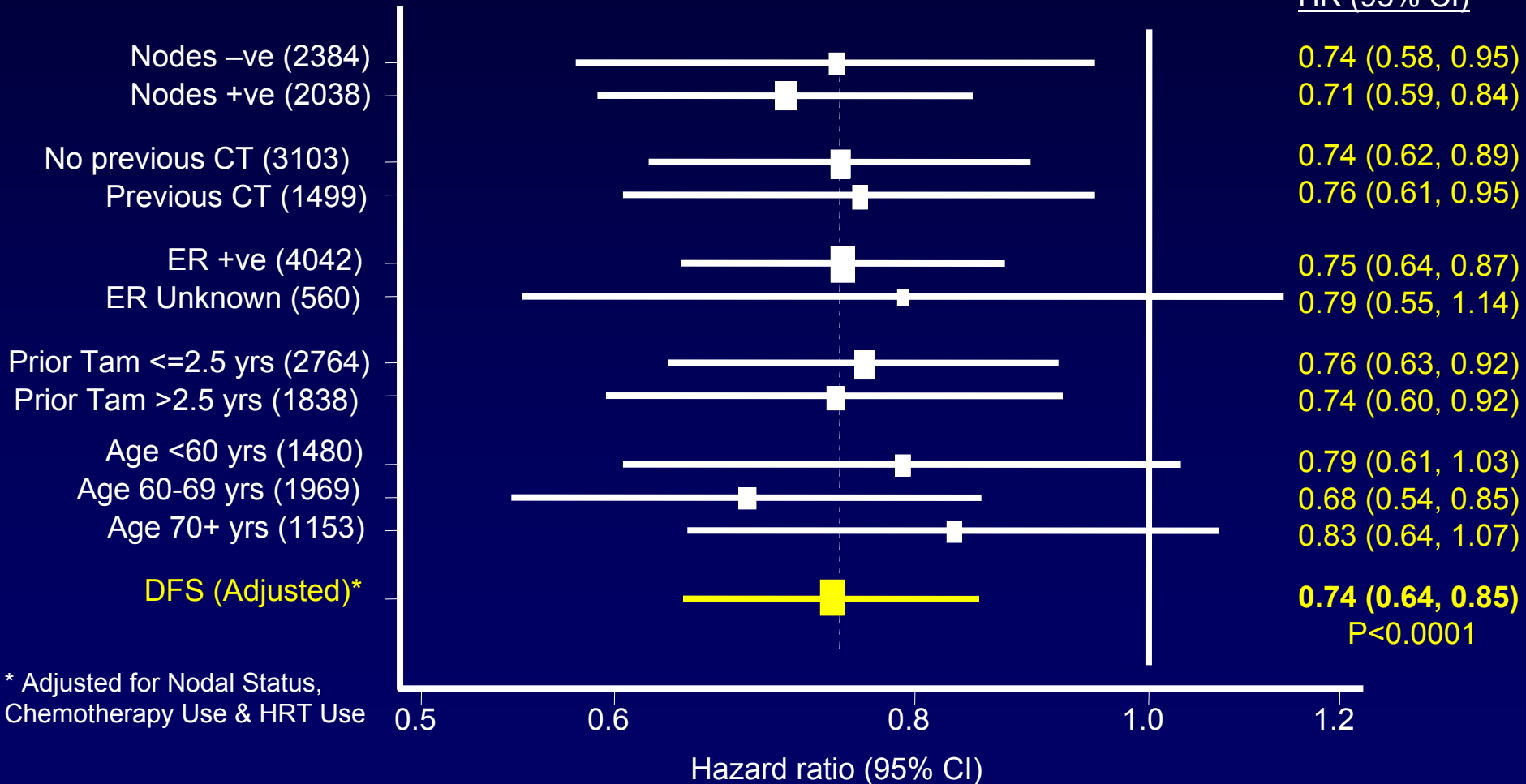
Is Exemestane Consistent Across Subgroups for Disease-Free Survival ?

Favors Exemestane

Favors Tamoxifen



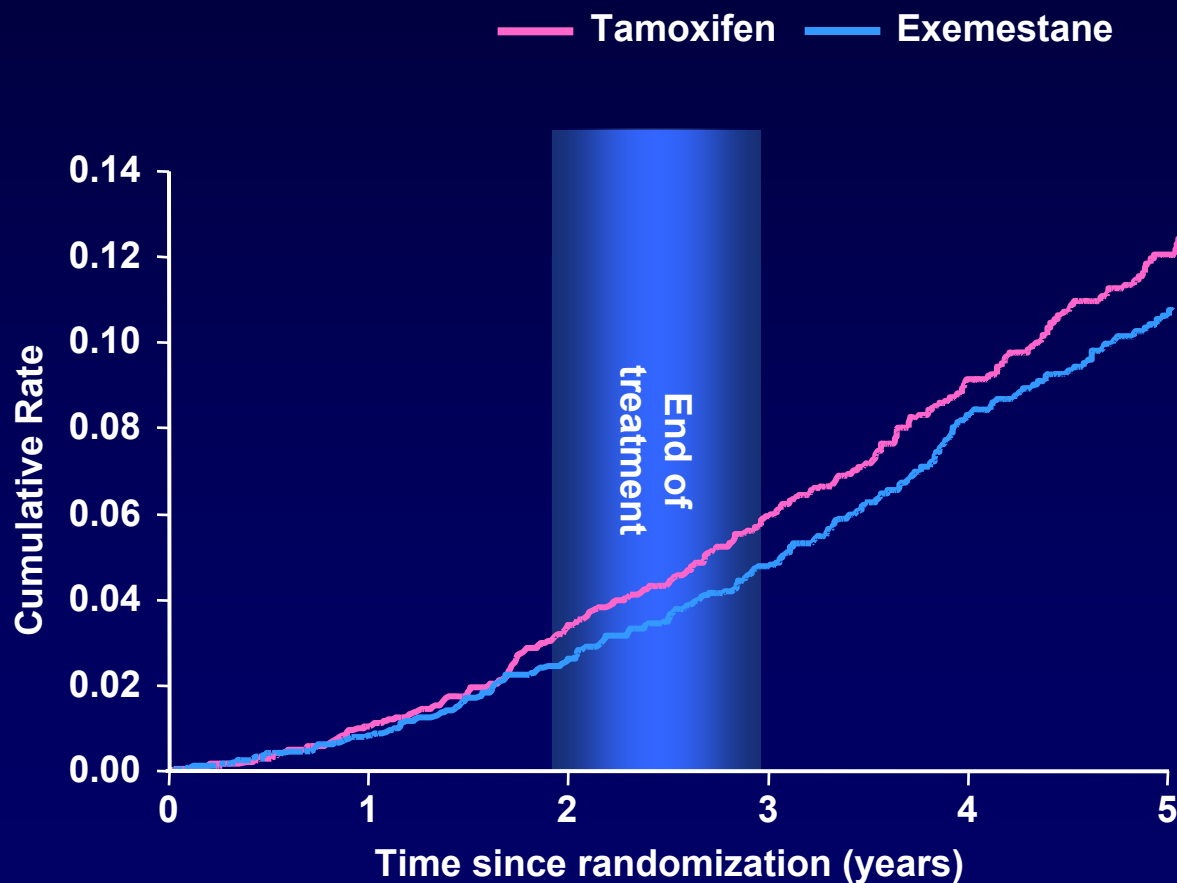
HR (95% CI)



* Adjusted for Nodal Status, Chemotherapy Use & HRT Use

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]

Tam / AI: Therapy Duration and Sequencing

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in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2008.1.1

	Oxford	/	AGO
	LoE	/	GR
➤ Tam 5 (instead of 2 or 1) yrs	1a	A	++
➤ Anastrozole or Letrozole 5 yrs**	1b	B	++
➤ For pts. being disease free after 2-3 yrs Tam:			
➤ Exemestane or Anastrozole***	1b	B	++
➤ Duration of AI up to 5 yrs	5	D	+/-*
➤ Re-Initiation Tam (if therapy < 5 yrs)***	2b	B	+

So far, no conclusive data to favour either upfront or sequential AI !

*study participation recommended

so far no OS advantage shown *up to a total of 5 yrs of endocrine therapy

Endocrine Therapy after 5 Years of Tamoxifen

Oxford / AGO
LoE / GR

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 +

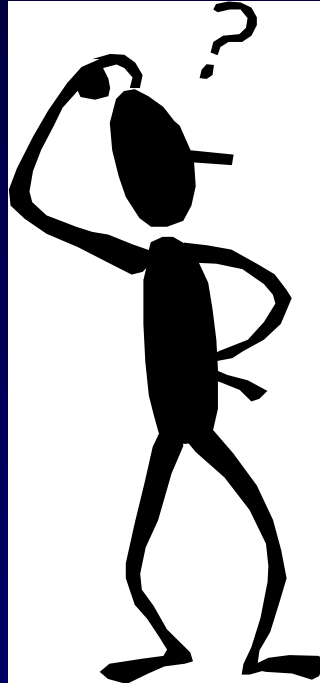
Exemestane 5 yrs

2b^a B +

Tam > 5 yrs

2b^a C +

Case #1: Side effects to discuss with endocrine therapy



Als 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

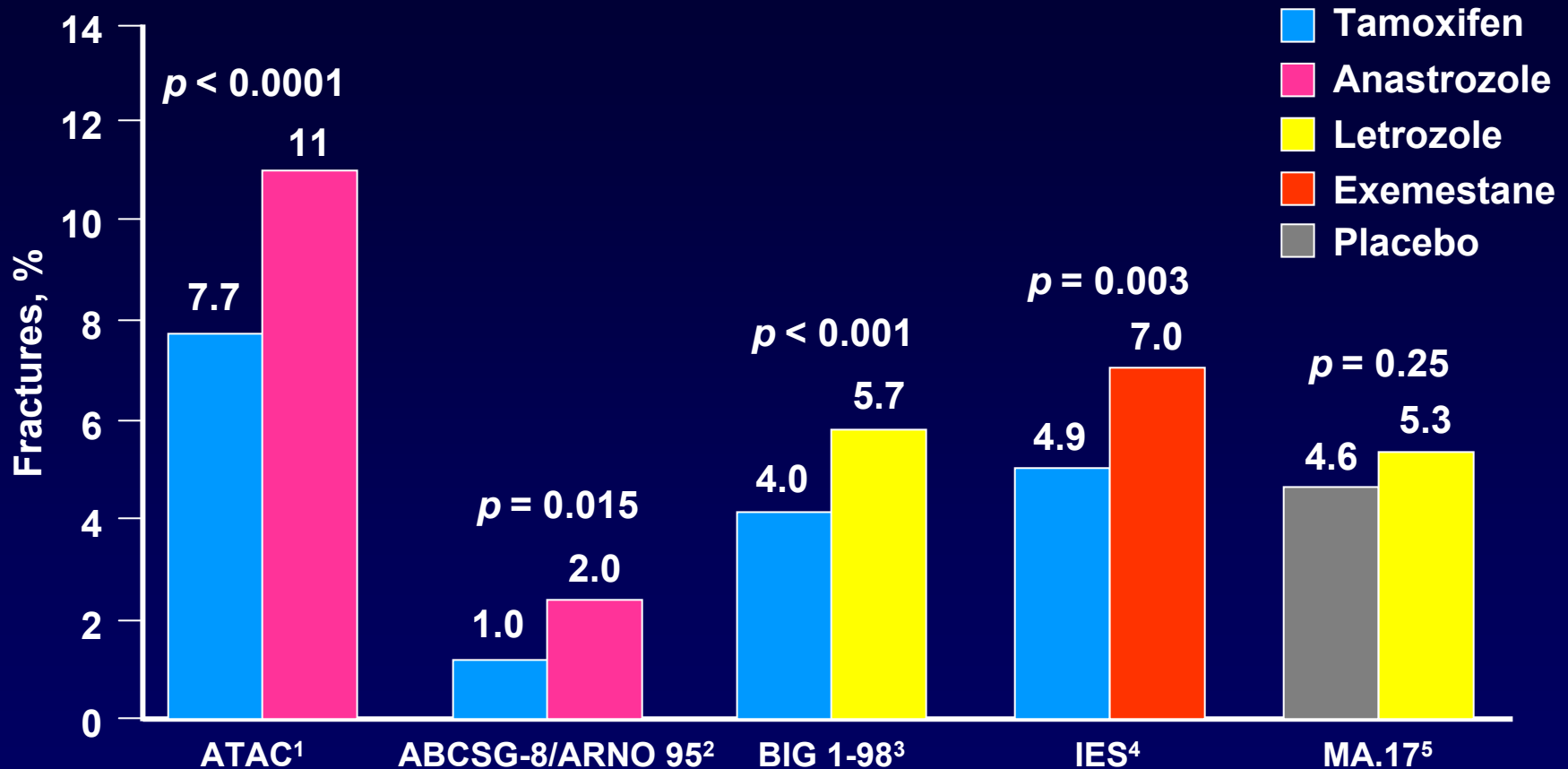
- ↑ Arthralgia/myalgia
- ↑ Osteoporosis risk

IES 031 Trial:

Patients with initially normal bone mineral density do not develop osteoporosis under 2-3 years of exemestane

Initial finding	Status after 2 years	Exemestane (n=101)	Tamoxifen (n=105)
Normal (n=52 E, n=59 T)	Normal bone	34 (65%)	46 (78%)
	Osteopenia	8 (15%)	3 (5%)
	Osteoporosis	0	0
	unknown	19 (7%)	10 (17%)
Osteopenia (n=49 E, n=46 T)	Normal bone	0	4 (9%)
	Osteopenia	36 (73%)	38 (83%)
	Osteoporosis	5 (10%)	0
	unknown	8 (16%)	4 (9%)

All AIs Increase Risk of Fracture

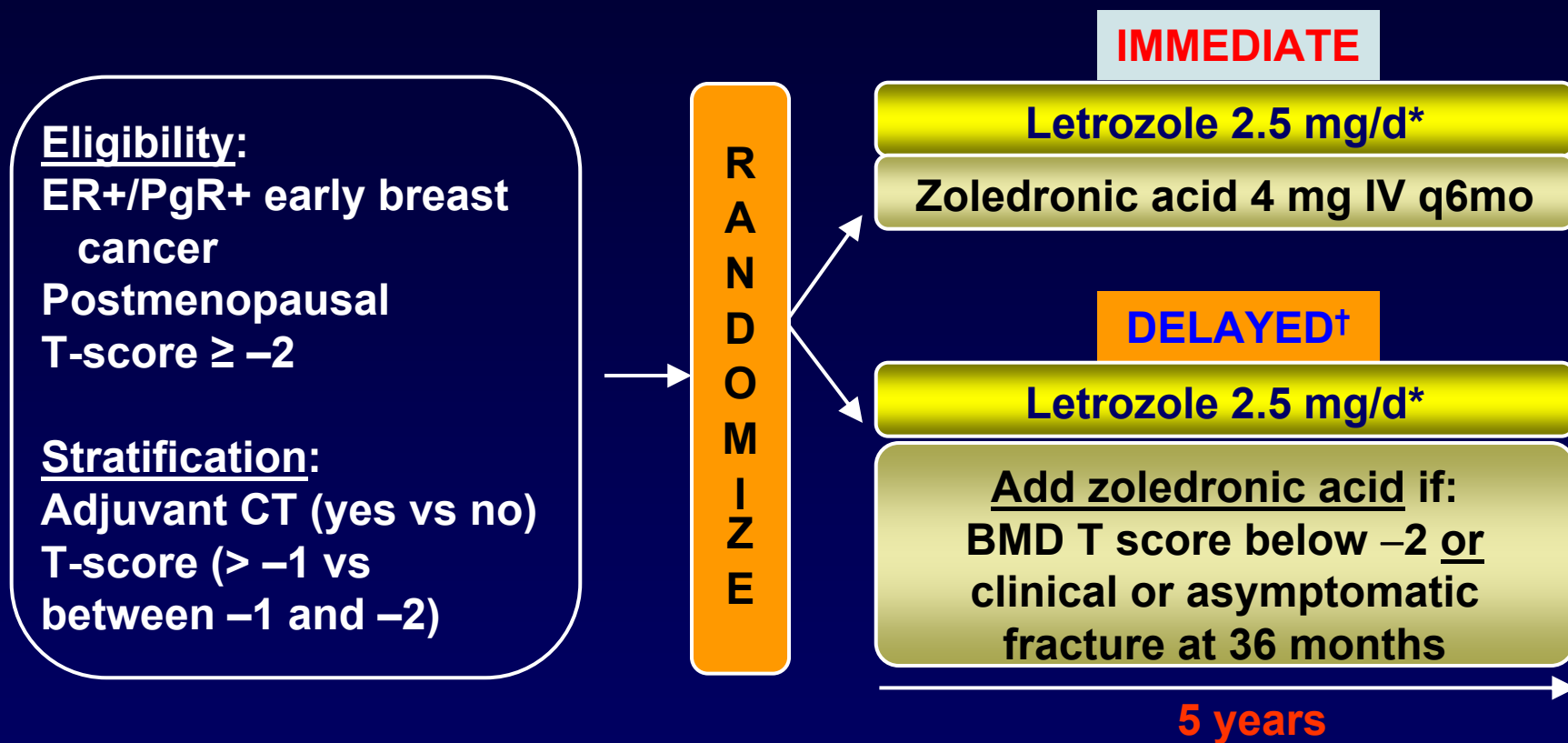


¹Howell et al. *Lancet* 2005;365:60-2. ²Jakesz et al. *Lancet* 2005;366:455-62.

³Thürlimann et al. *N Engl J Med* 2005;355:2747-57. ⁴Coombes et al. *Lancet* 2007;369:559-70.

⁵Goss et al. *J Natl Cancer Inst* 2005;97:1262-71.

Z/ZO-FAST Trial Design

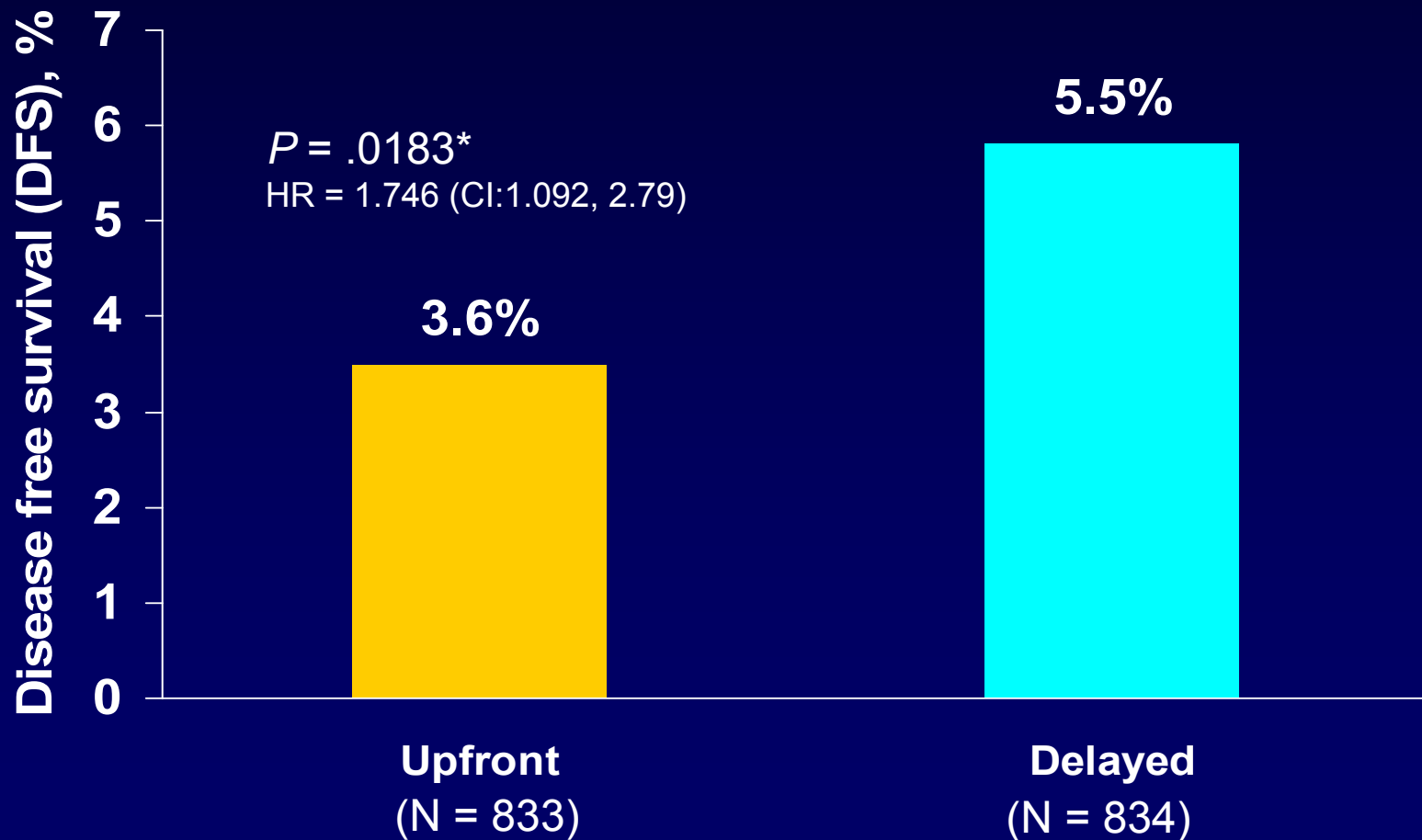


Accrual complete: ZO-FAST: N=1066; Z-FAST: N=602.

* Plus daily calcium (1000-1200 mg) and vitamin D (400-800 IU).

† Initiation determined by a post-baseline T-score below -2 , any clinical fracture, or asymptomatic fracture at 36 months

Disease Free-Survival: Z/ZO-FAST 24 Month Integrated Analysis



Bisphosphonates in Breast Cancer

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➤ Hypercalcemia	1a	A	++
➤ Bone metastasis	1a	A	++
➤ Tumor-therapy-induced osteopenia	1b	B	++
➤ Prevention of bone metastases			
➤ Primary breast cancer	1b(-)	B	+*
➤ Advanced breast cancer	2b	C	+/-
➤ Prevention of bone loss in patients with increased risk of osteoporosis	2b	C	+
➤ Treatment beyond progression	5	D	++

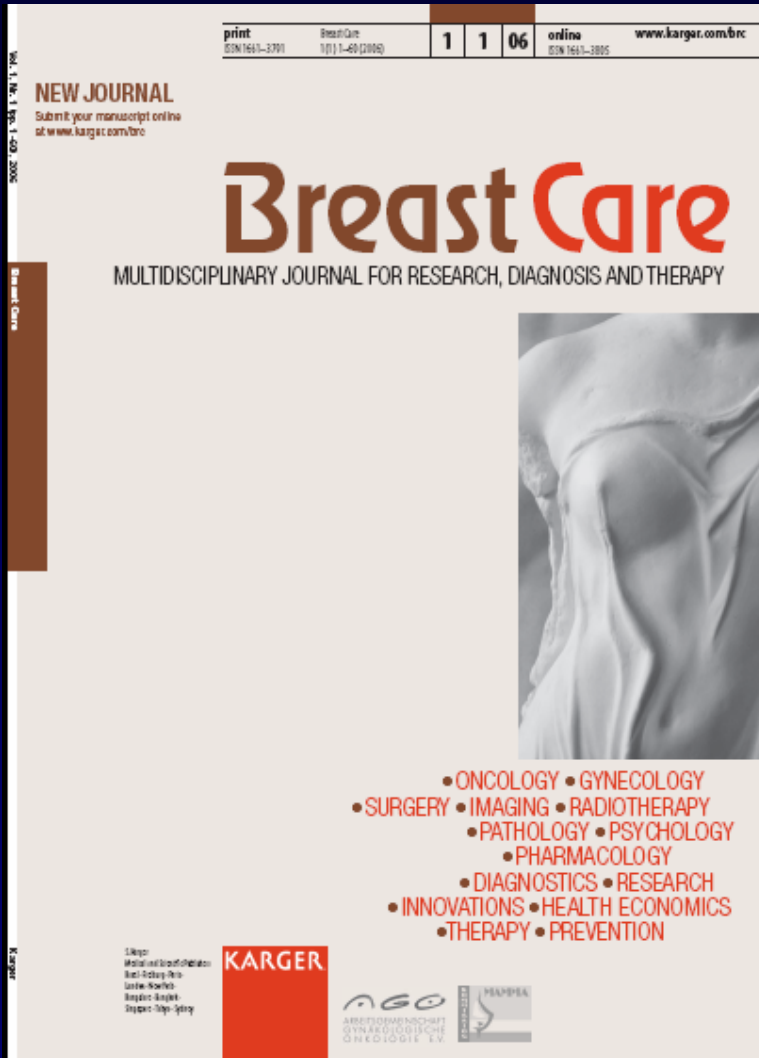
Side effects of bisphosphonates see chapter

* Study participation recommended

Case #1: My opinion

- 60 year old postmenopausal patient (ECOG 0):
pT1c, **pN0 (sn)**, **G2**, ER (70%) and PR (40%)
positive, HER2 negative
- **Adequate risk assessment:**
 - uPA/PAI-1 test
 - If low risk: 2 years of TAM, then switch to AI
 - If high risk: Chemotherapy (NNBC-3 trial), then AI for 5 years, consider adjuvant bisphosphonates
 - Consider bone health (bone density measurement before endocrine therapy)

Evidence-based Breast Cancer Therapy



AGO (DKG, DGGG)
www.ago-online.org

www.karger.com/brc