

Endocrine-Responsive Early Breast Cancer: Decision Making for the Postmenopausal Patient

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Determining Risk of Recurrence

Adjuvant! Online estimation

St Gallen criteria

**21-gene recurrence score assay
(Oncotype DX®)**

70-gene array profile

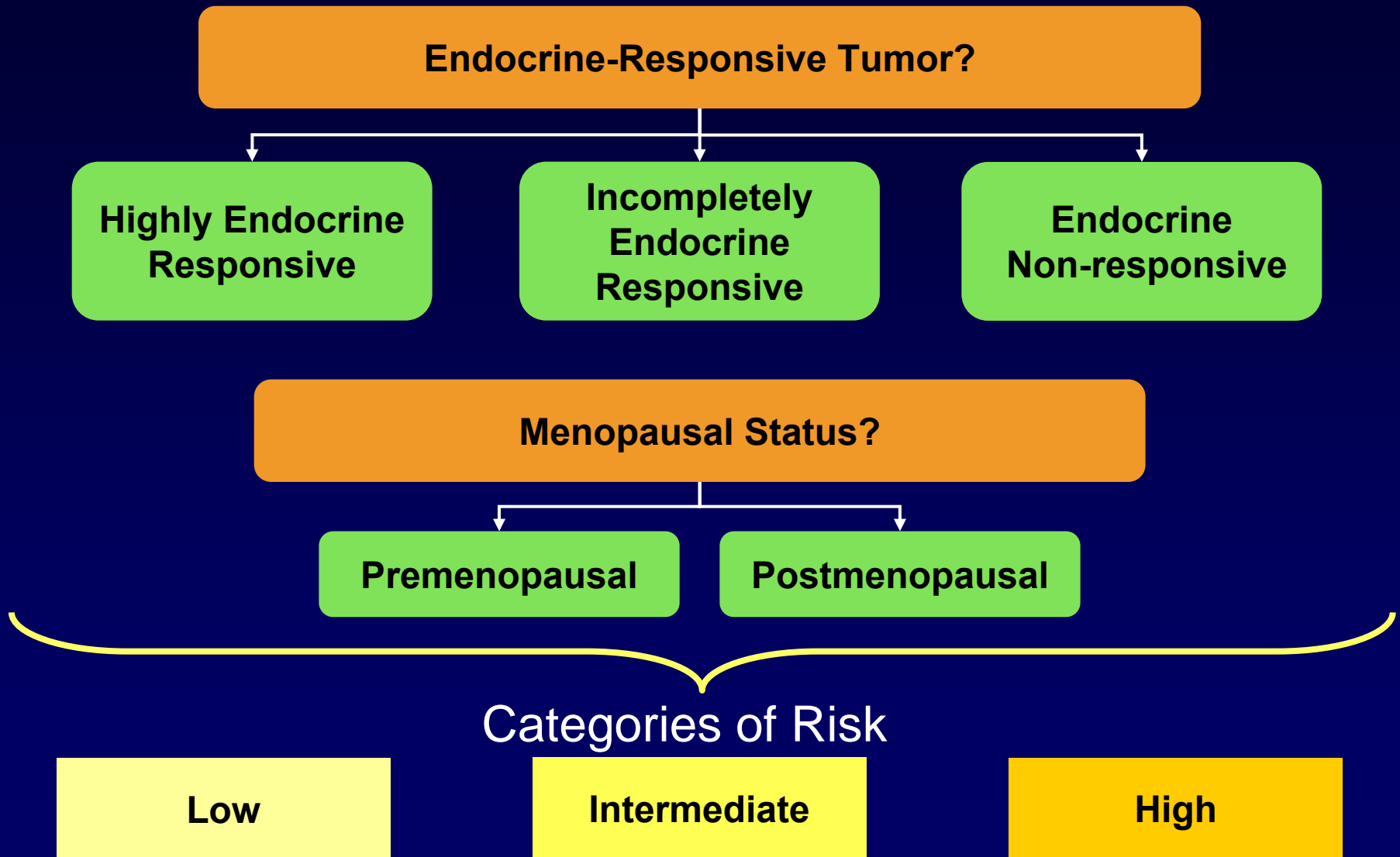
MINDACT

TAILORx

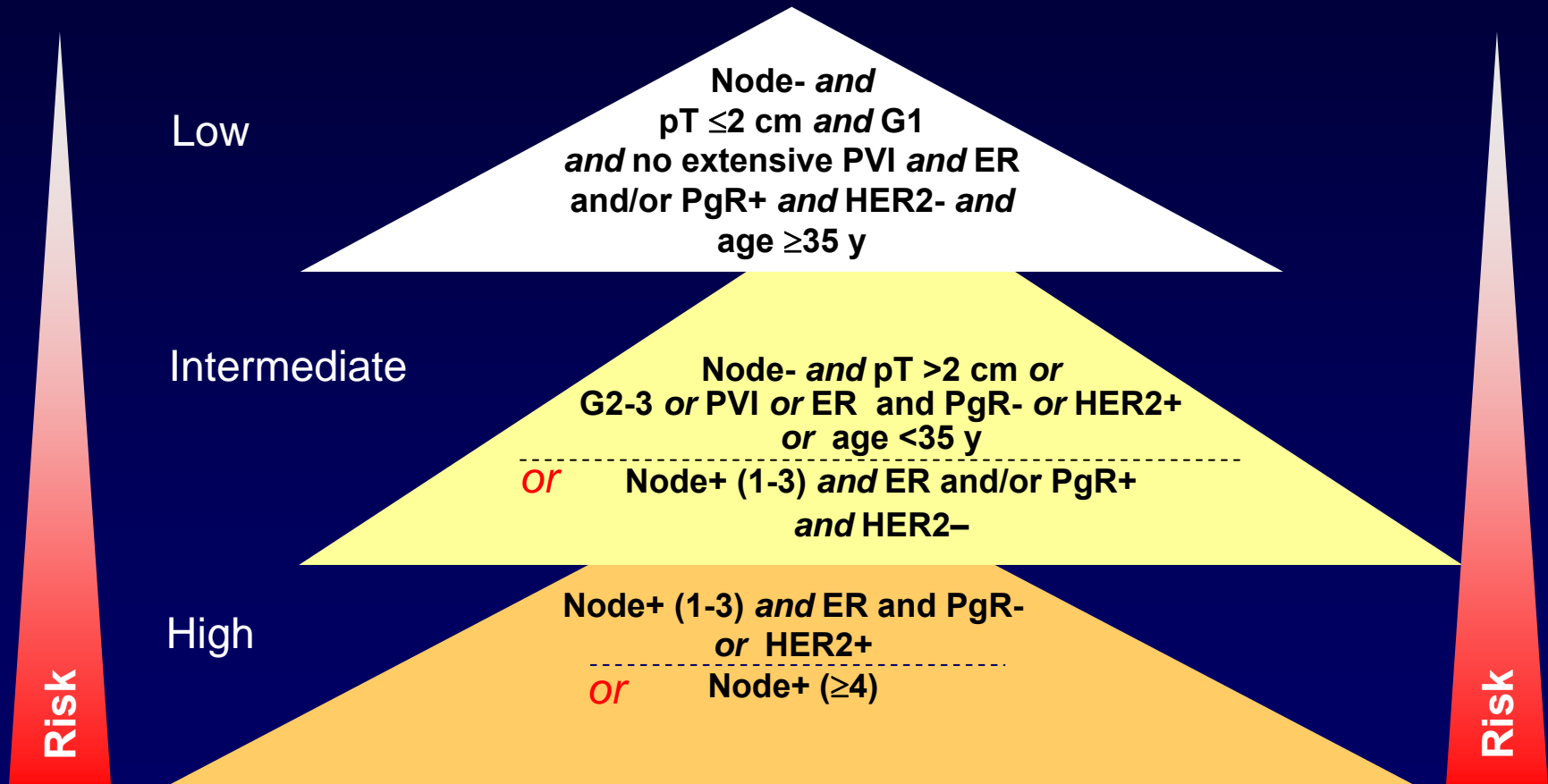
Adjuvant! Online

- Risk of relapse is low
- Benefit with adjuvant endocrine therapy
- Added benefit of chemotherapy is minimal

Risk of Recurrence in Early Breast Cancer: St. Gallen 2007 — Considerations in Evaluating Risk



Risk of Recurrence in Early Breast Cancer: St. Gallen 2007 — Revised Definitions of Risk



pT = pathologic tumor size; G = grade (histologic and/or nuclear) ; PVI = peritumoral vascular invasion.

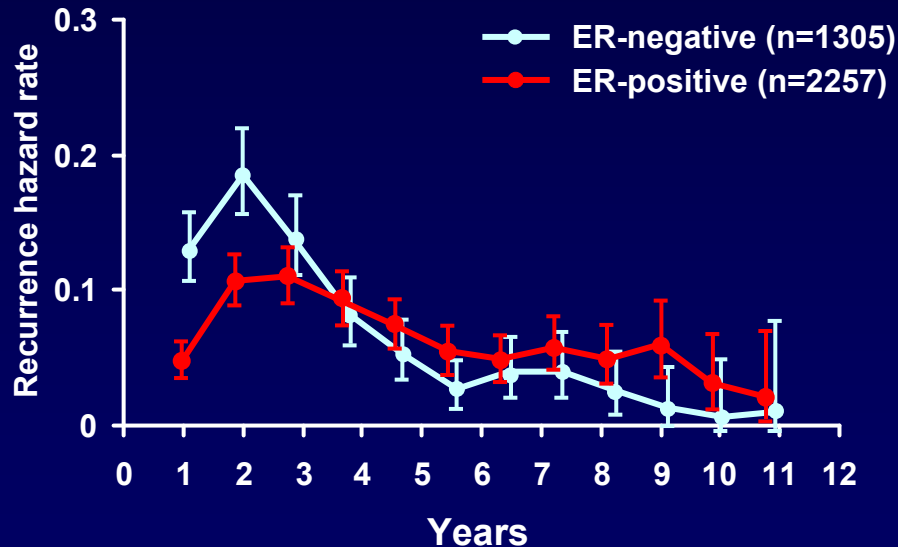
Adapted with permission from Piccart-Gebhart MJ. Plenary presentation. SABCS; 2005; San Antonio, Tex.
Goldhirsch A et al. *Ann Oncol.* 2007;18:1133-1144.

21 Gene Recurrence Score (Oncotype DX®)

- RS has been validated for estimating residual risk of distant recurrence in ER+, node negative breast cancer receiving tamoxifen
- Trans-ATAC, Dowsett San Antonio 2008, 1231 patients, 872 node negative
- Multivariate analysis tumour size, grade and RS predictive of DR
- RS showed statistically significant prognostic value beyond adjuvant on line
- 21 gene RS is an independent predictor of risk of DR in patients treated with Tamoxifen or Anastrozole

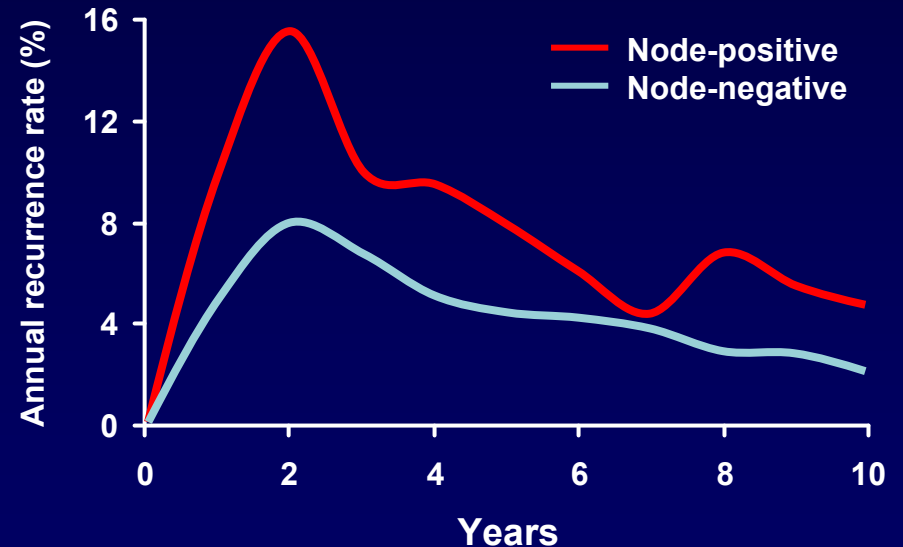
Risk of Recurrence

Annual Hazard of Recurrence by Estrogen Receptor Status¹



Risk of Recurrence by Nodal Status

- Untreated patients in EBCTG 1998 meta-analysis^{2,3}

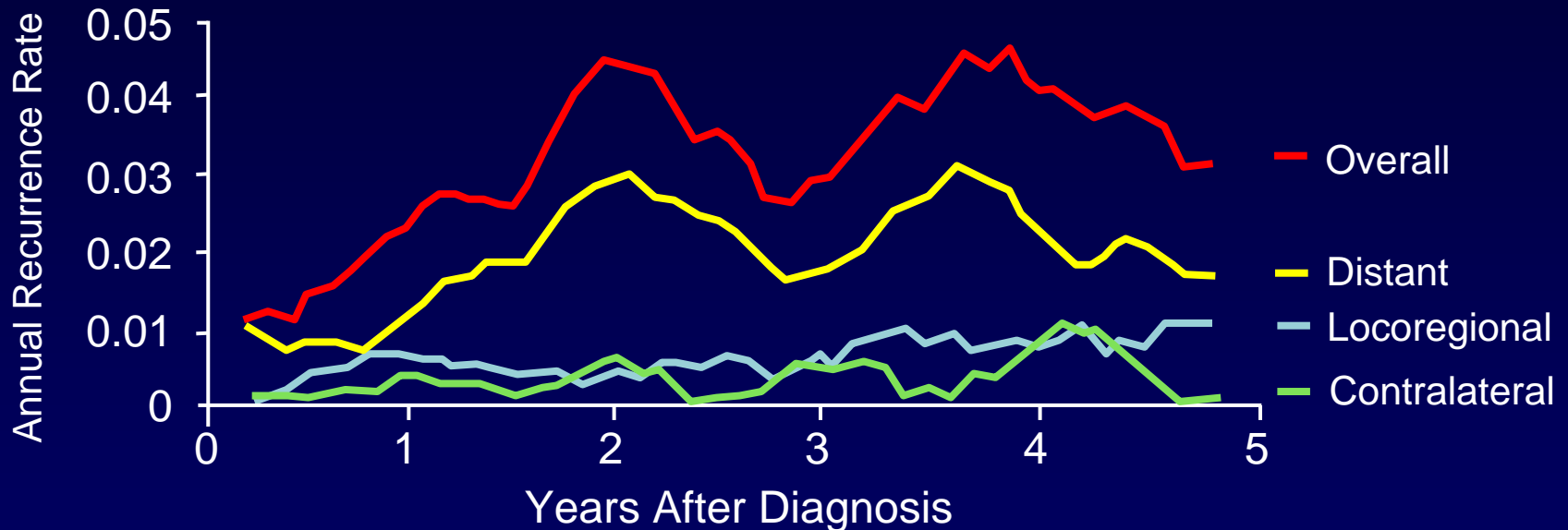


1. Saphner et al. *J Clin Oncol*. 1996;14:2738.

2. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1998;351:1451.

3. Update of Houghton. *J Clin Oncol*. 2005;23(16S):24s. Abstract 582.

ER+ Overall Annual Recurrence Rates (Including Recurrence Types)



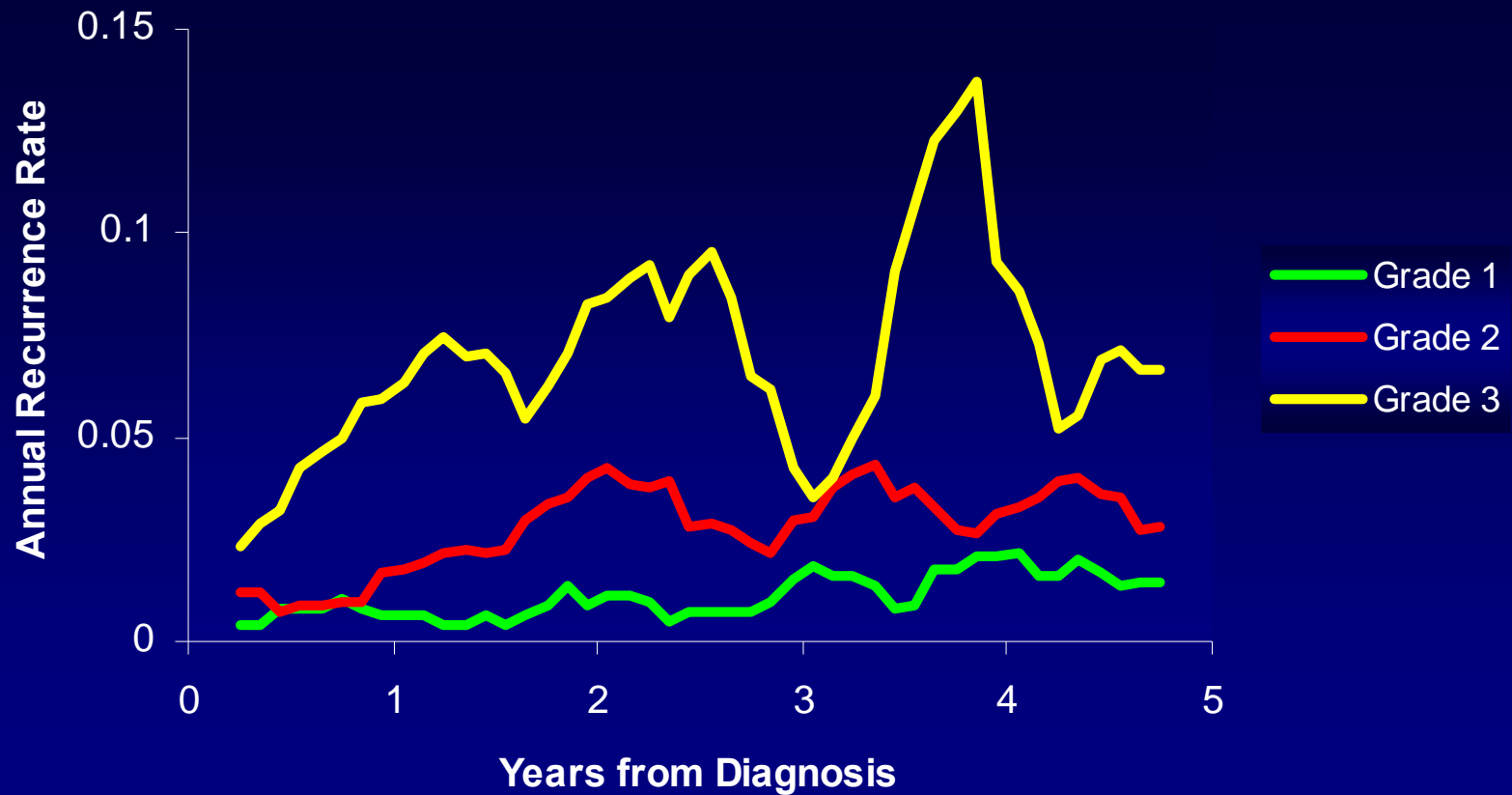
5589 PM women from 1995-2004c

Distant recurrences are responsible for the initial peak of recurrences seen at 2 years:
Age, tumour size, grade, node status, LVI all predict for early recurrence

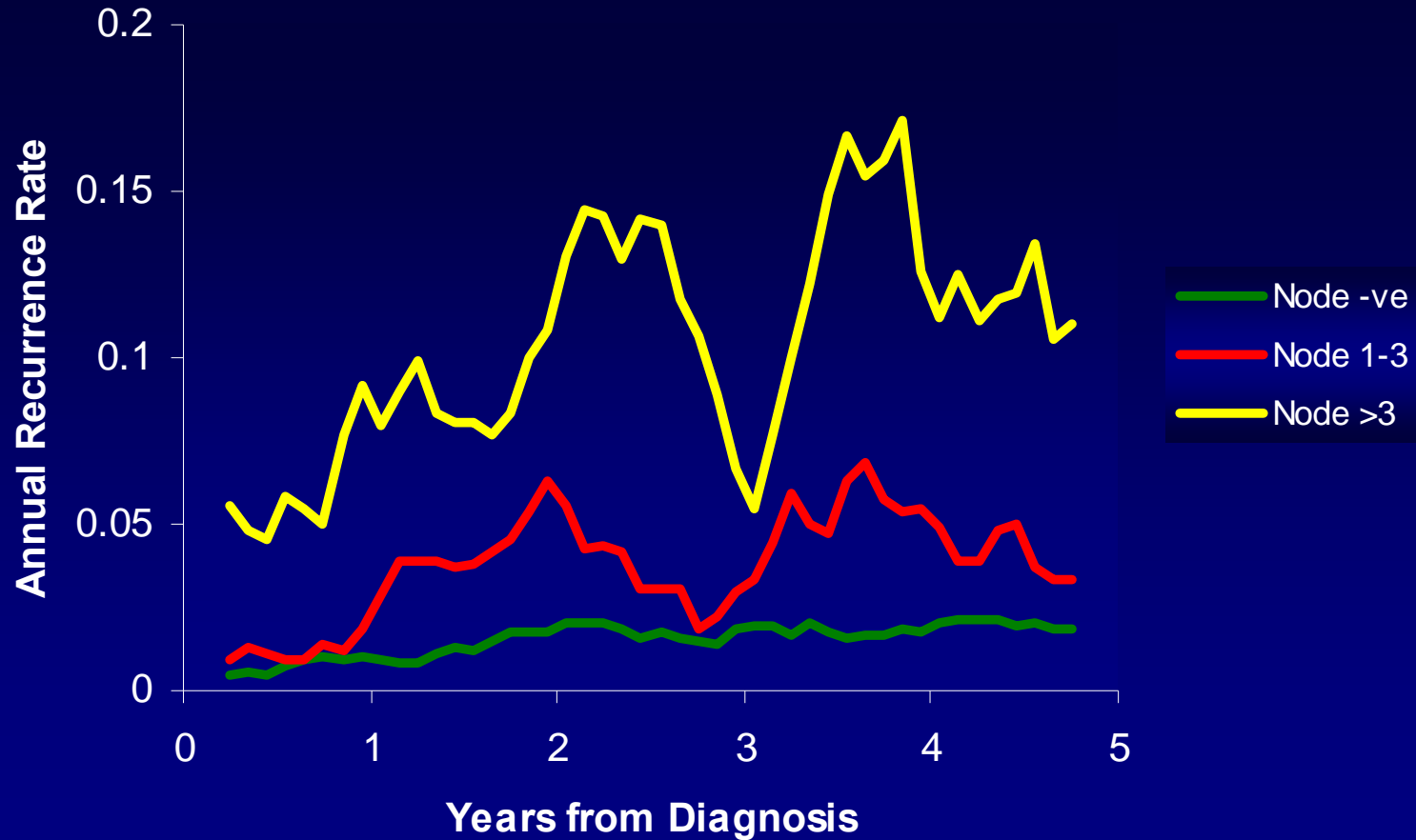
Mansell J et al. Presented at: SABCS 2006, San Antonio, Tex. Abstract 2091.

Updated man available: Mansell J et al. *Breast Cancer Res Treat*, epub ahead of print 2008 Dec 27.

ER+ Annual Distant Recurrence Risk By Grade

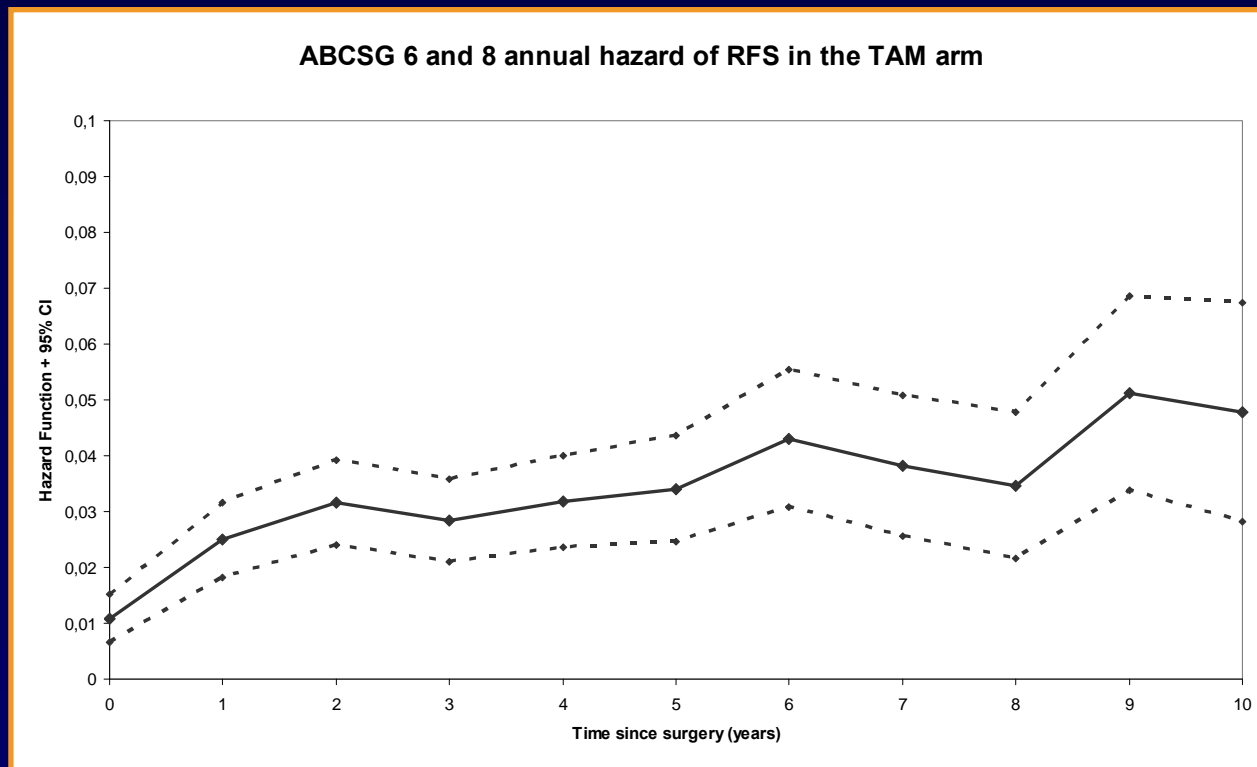


ER+ Annual Distant Recurrence Risk By Nodal Status



TAM and ANA as a Sequencing Strategy in Postmenopausal Women: An Update of ABCSG-8

- The major concern in interpreting the value of the switching strategy is the exclusion of events in the first two years.

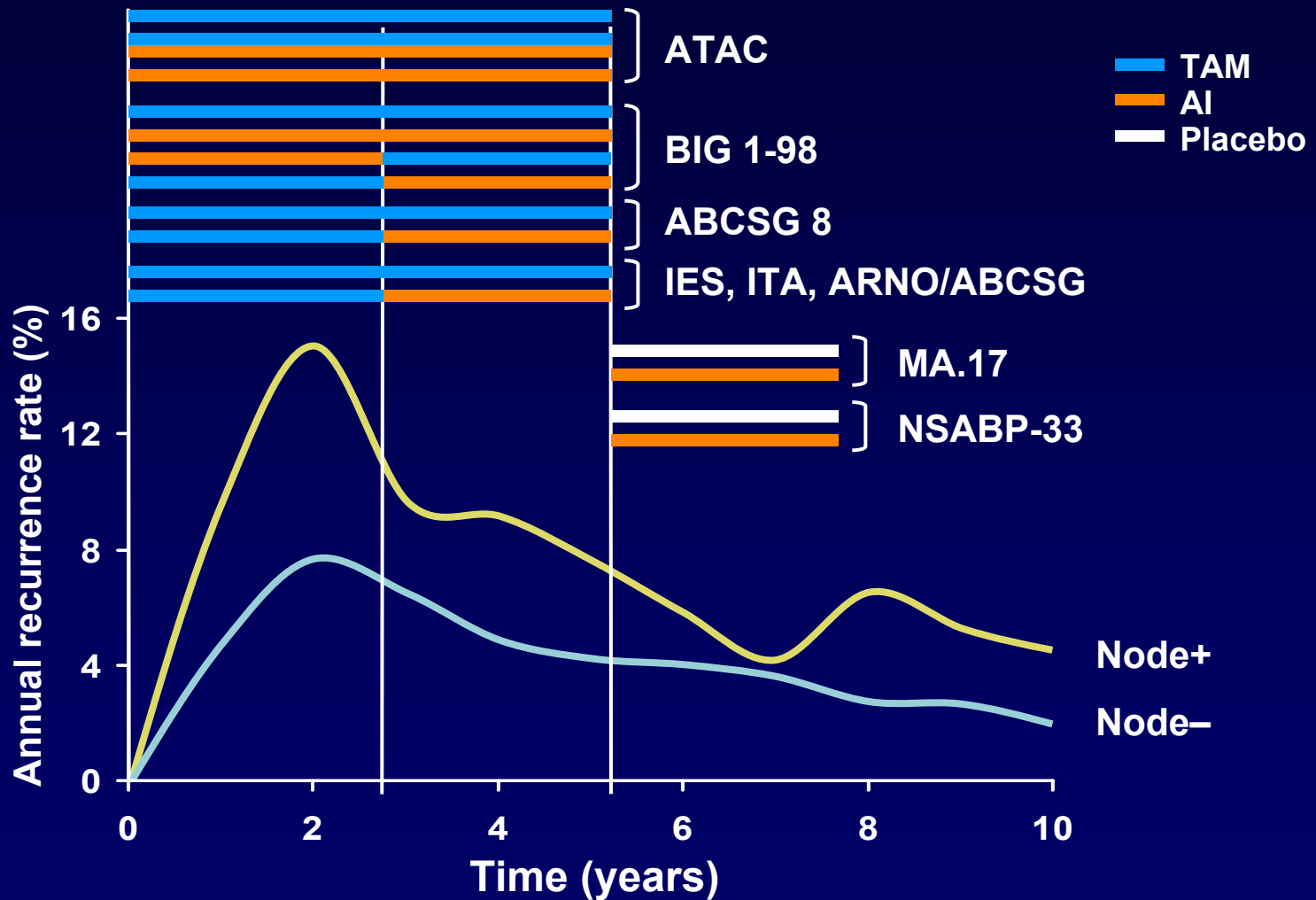


ductal G1,2,
lobular tumor
type

n=2192

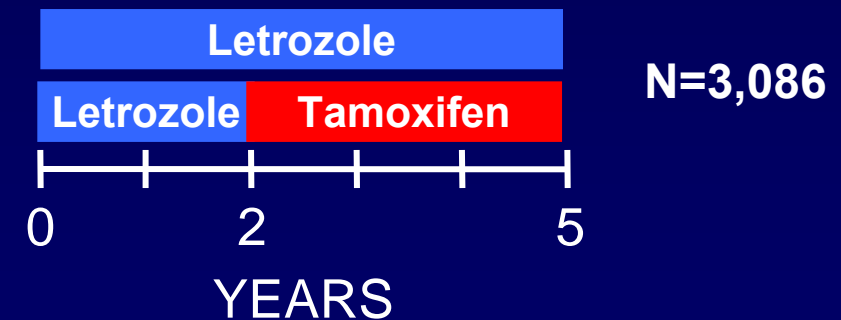
median follow-
up: 100 months

Effect of Adjuvant AIs on Distant Disease: Different Strategies



BIG 1-98 Sequential Therapy Two Pairwise Comparisons

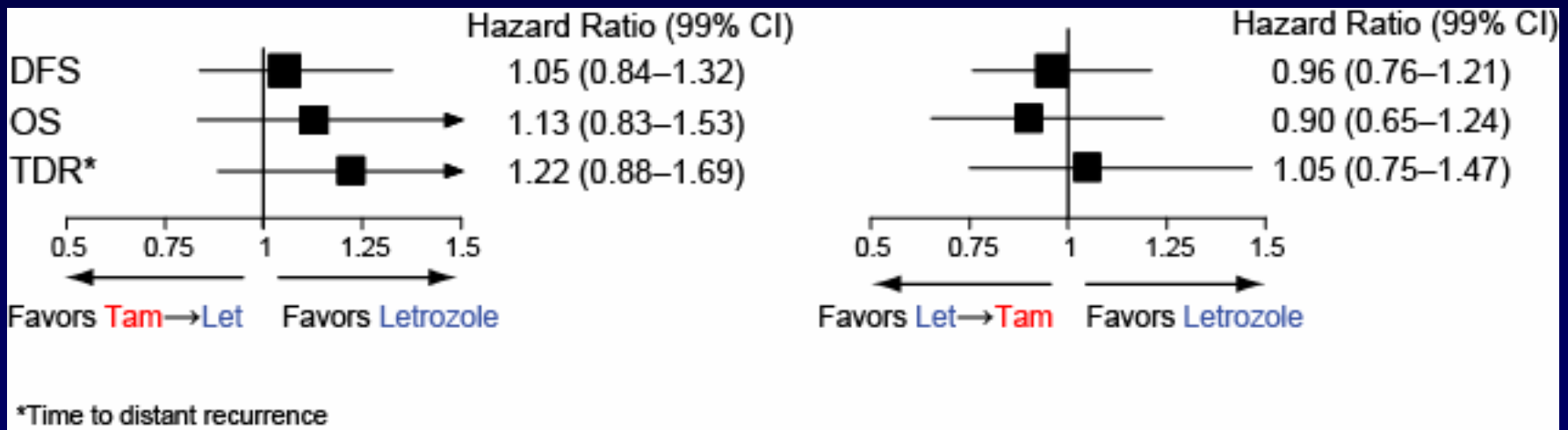
- 3 blinded arms
- Sequential vs. letrozole monotherapy
- Evaluated from randomization
- Median Follow Up 71 mos.
- 99% confidence intervals to account for multiple comparisons



Sequential Treatment Comparisons Median Follow-up 71 months

Tam→**Let** vs. **Let**

Let→**Tam** vs. **Let**

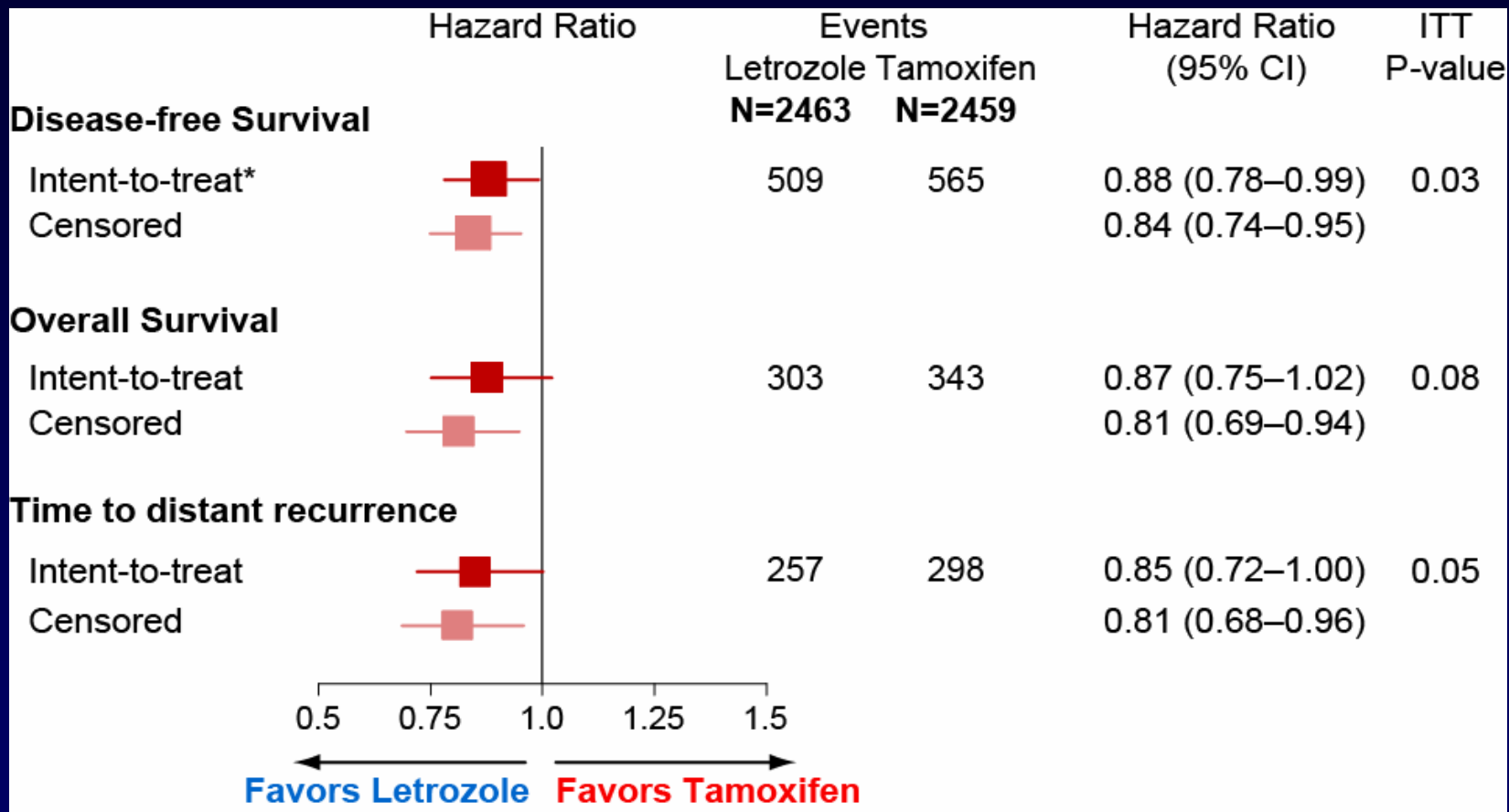


BIG 1-98 Monotherapy Update

- 2005 results of Let superiority led to unblinding of Tam-alone arm
- 619 (25.2%) patients selectively crossed over to Let
 - Mostly in years 3-5
 - Median duration Let after crossover 18 mos.
- This complicates comparisons with Tam alone
- The comparison of Tam vs. Let was done by
 - Intent-to-treat (ITT)
 - Censoring at crossover

BIG 1-98 Monotherapy Update

Median Follow-up 76 months



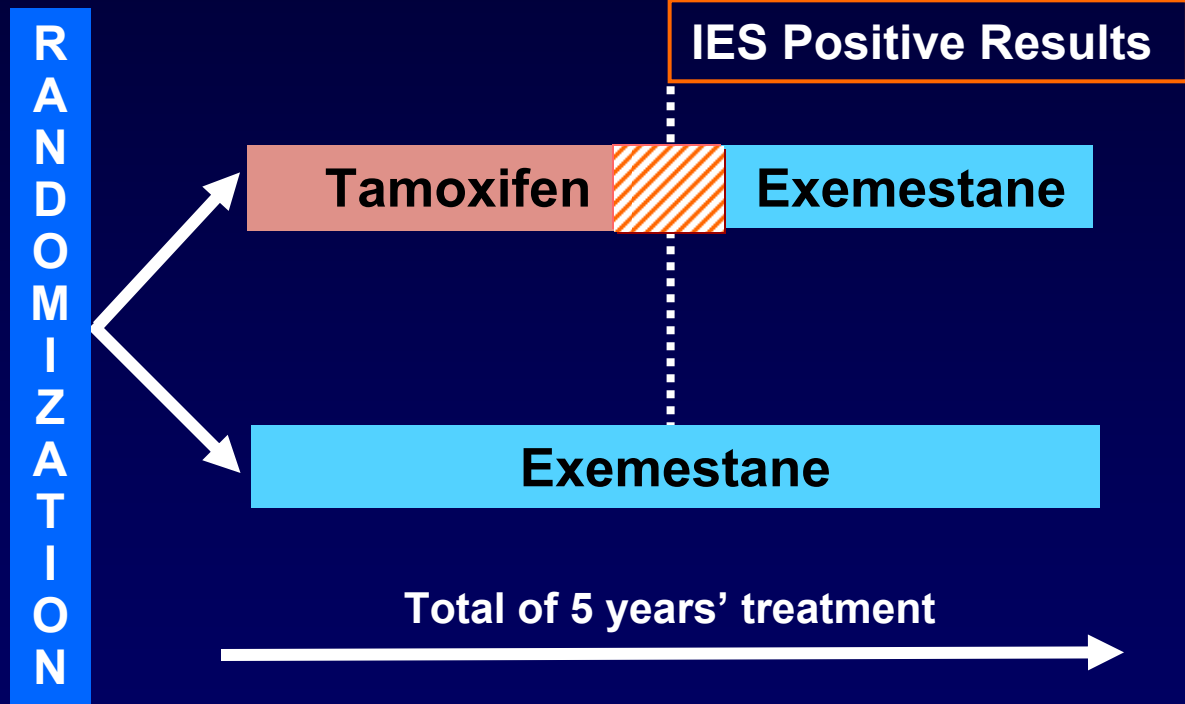
*Let:Tam: breast cancer events, 321:363
 second (non breast) malignancy, 101:115
 deaths without prior cancer event, 87:87

TEAM Trial: Revised Design 2004

N = 9775 accrued

Postmenopausal
receptor-positive
women

Diagnosis and
adequate primary
therapy of early
breast cancer



IES Positive Results

Tamoxifen

Exemestane

Exemestane

Total of 5 years' treatment

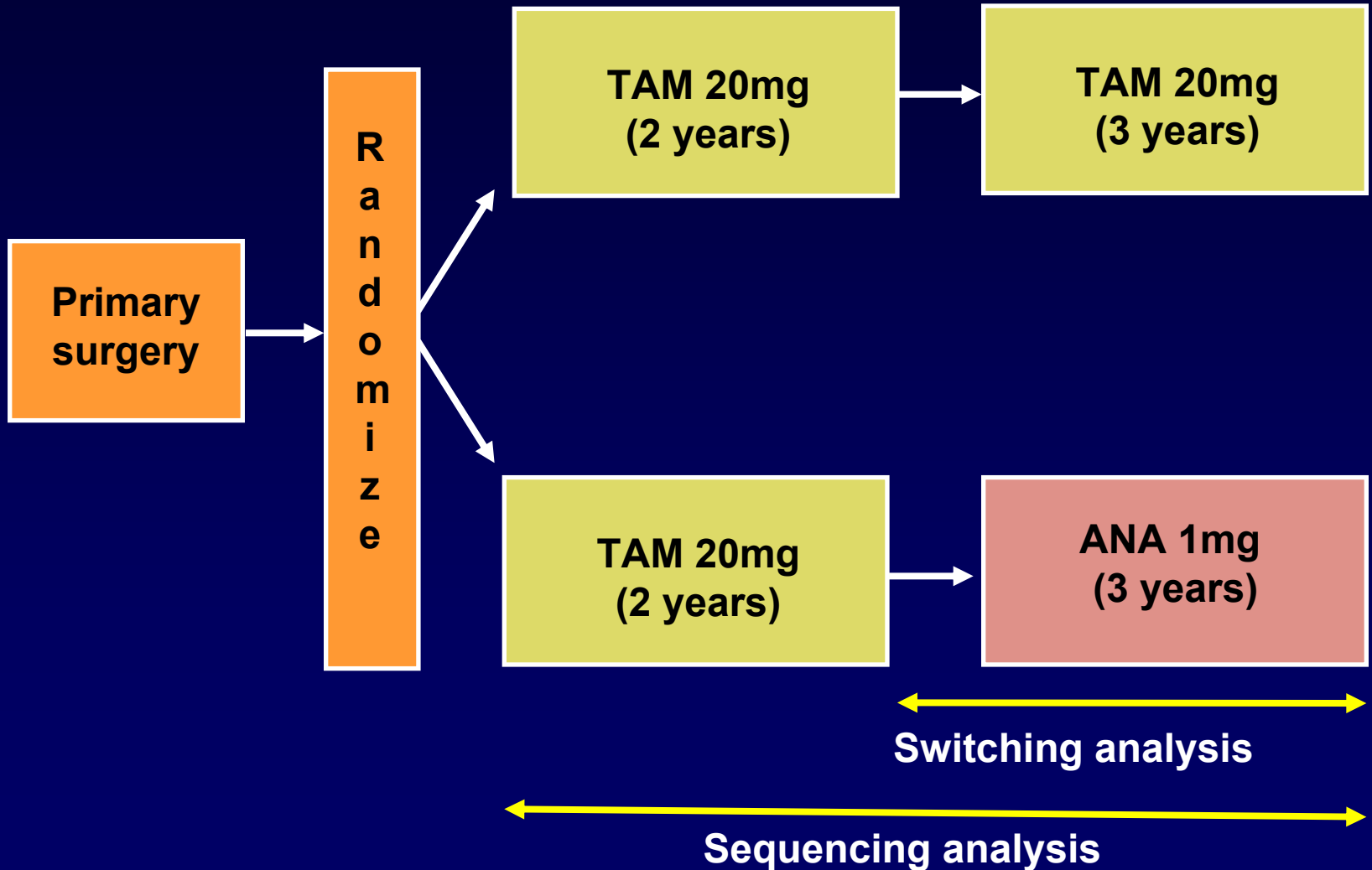
Co-primary end points

DFS at 2.75 years
DFS at 5 years

Conclusions of TEAM Trial at 2.75 Years

- **Exemestane was associated with improvement in:**
 - **Disease-free survival (HR: 0.89; $P=0.12$)**
 - **On-study drug disease-free survival (HR 0.83; $P=0.02$)**
 - **Relapse-free survival: (HR: 0.85; $P = 0.02$)**
 - **Time to distant metastases (HR: 0.81; $P<0.02$)**

ABCESG Trial 8 Structure



ABCSG Trial 8 Inclusion Criteria

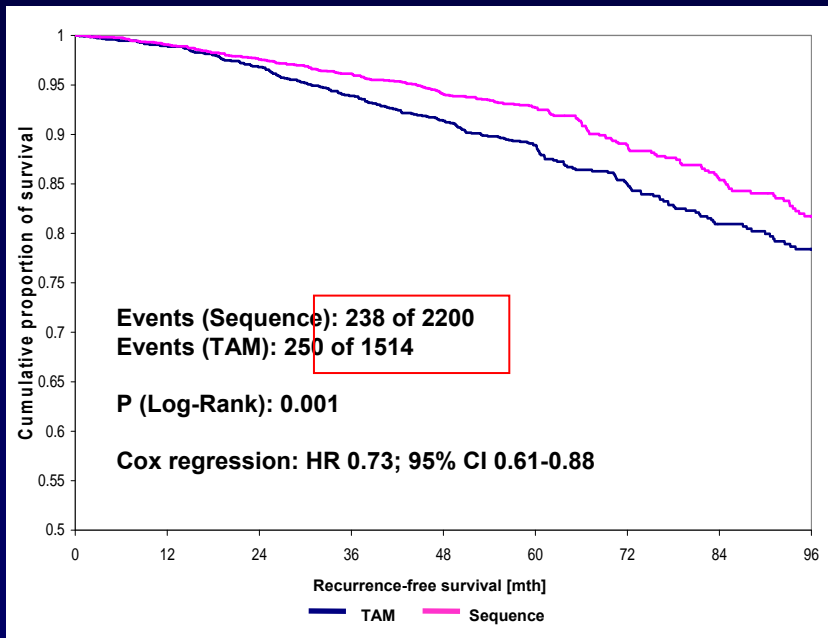
- Postmenopausal patients with operable breast cancer (within 3 years after cessation of menses according to hormone profile)
- ≤ 80 years old ← **This is different from other trials**
- ER+ / PgR+
- Ductal G_{1,2} and lobular breast cancer type ← **This is different from other trials**
- Modified radical mastectomy or conservative breast surgery
- Lymph node surgery (sentinel node or axillary node dissection)
- Chemotherapy not permitted ← **This is different from other trials**

ER+, estrogen receptor-positive;
PgR+, progesterone receptor-positive

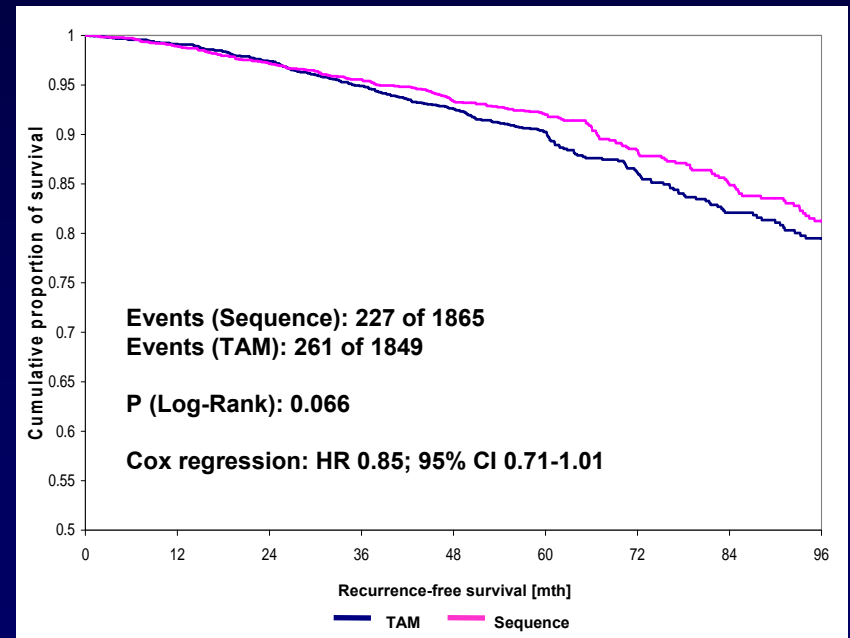
ABCSG Trial 8: RFS

Total sample

Retrospective



Cross-over censored



Conclusion

- **This trial, investigating the sequence of TAM followed by ANA, shows a disease-free survival (DFS) benefit over 5 years of adjuvant TAM**
- **A benefit in OS favoring the sequential therapy over TAM alone is seen but must await peer-reviewed manuscript before drawing final conclusion**
- **Further research is needed to define the optimal strategies for individual patients and patient subgroups**

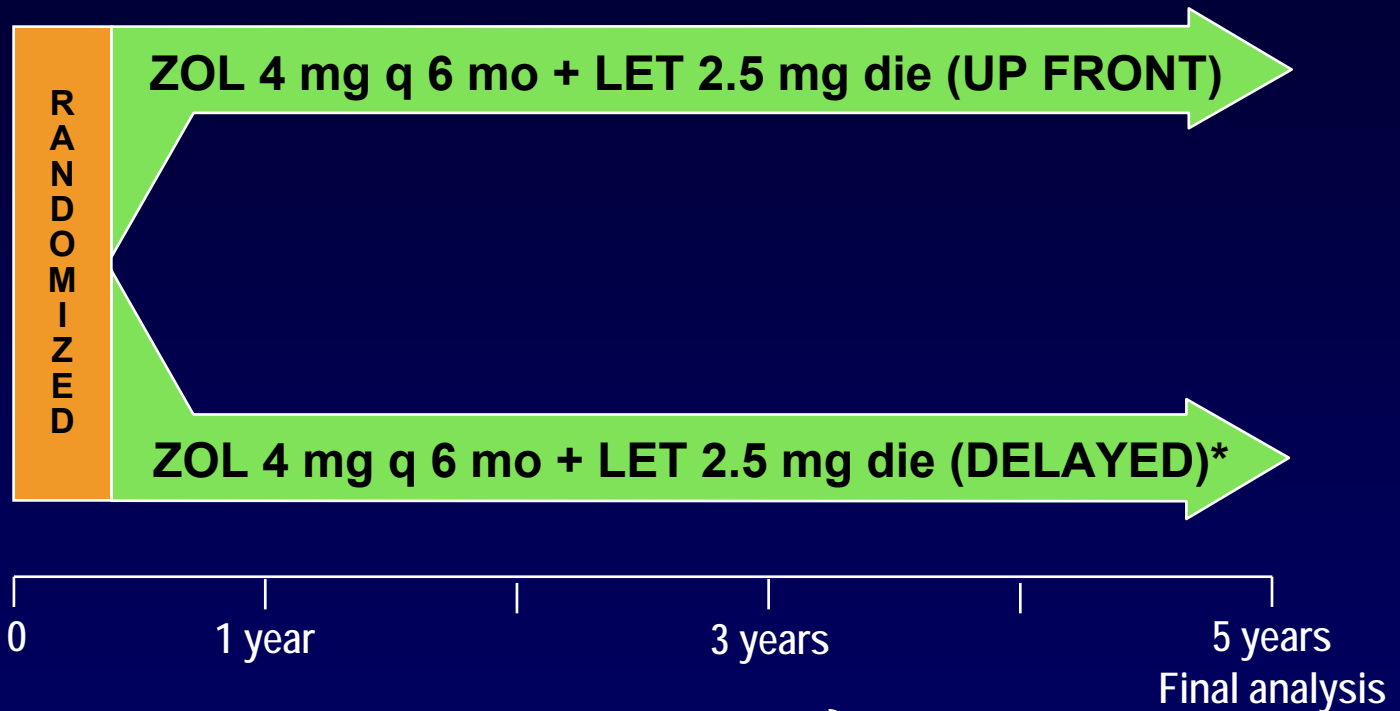
Z-FAST,¹ ZO-FAST², and E-ZO-FAST³ Study Design

Eligibility

- ER⁺/PgR⁺ BCa
- PMW with T-score ≥ -2

Stratification

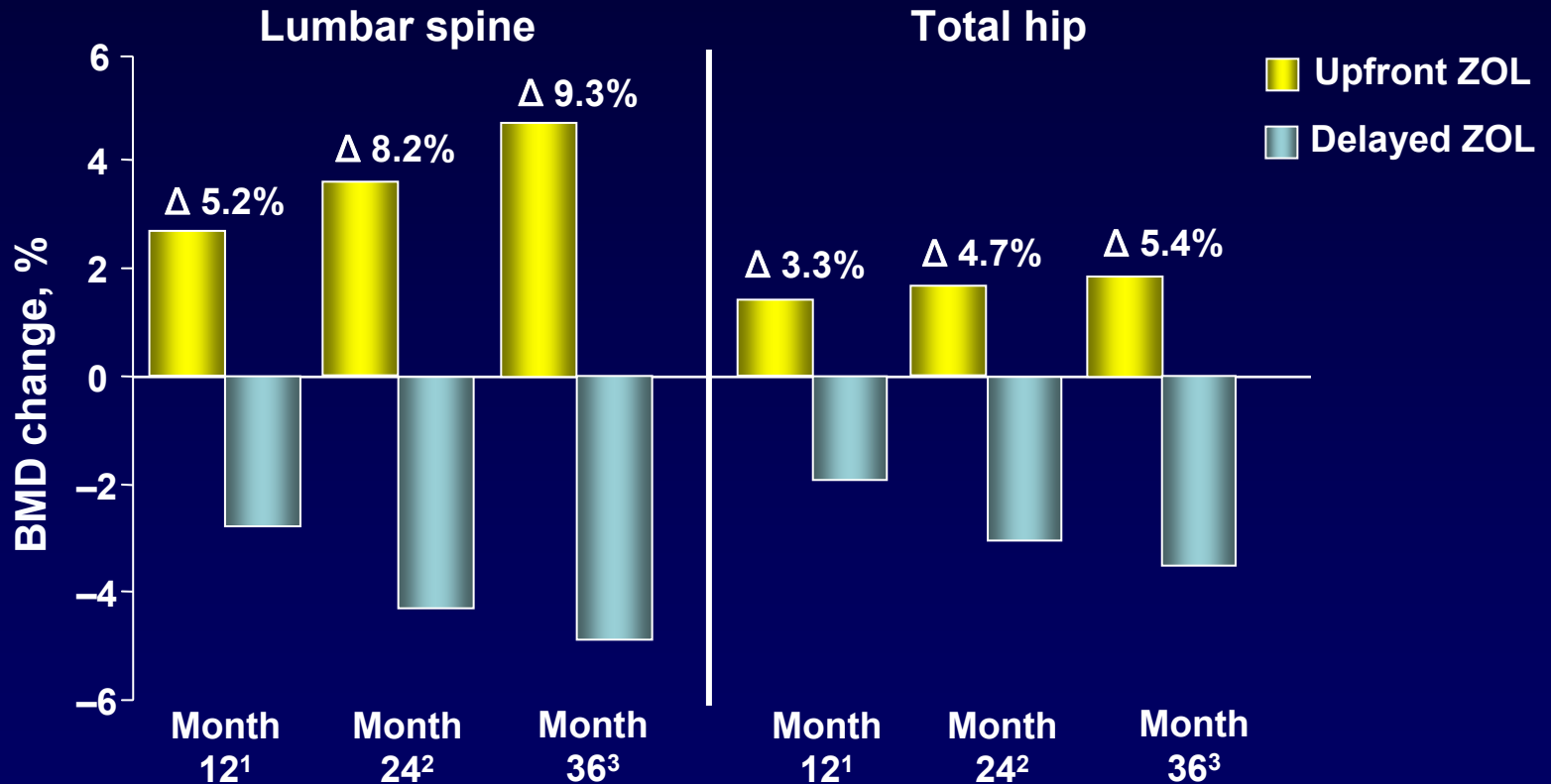
- Adjuvant CT (yes or no)
- T score (> -1 or between -1 and -2)



Accrual completed: Z-FAST: N = 602
ZO-FAST: N = 1,066 } **2,194**
E-ZO-FAST: N = 526

ZO-FAST—Upfront Zoledronic Acid Increased BMD in Lumbar Spine and Hip (N = 1,064)³

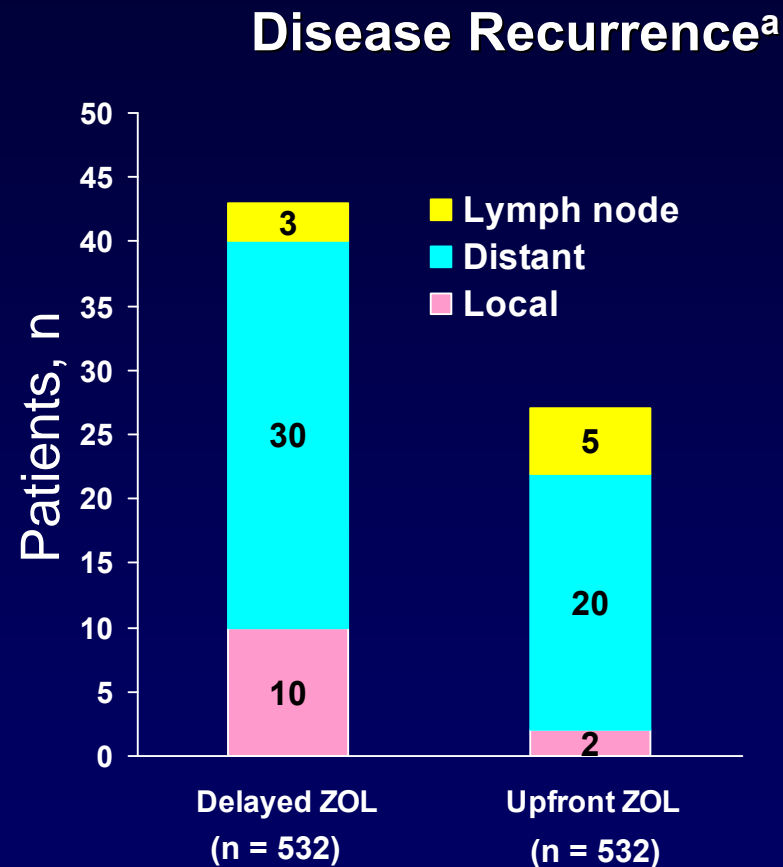
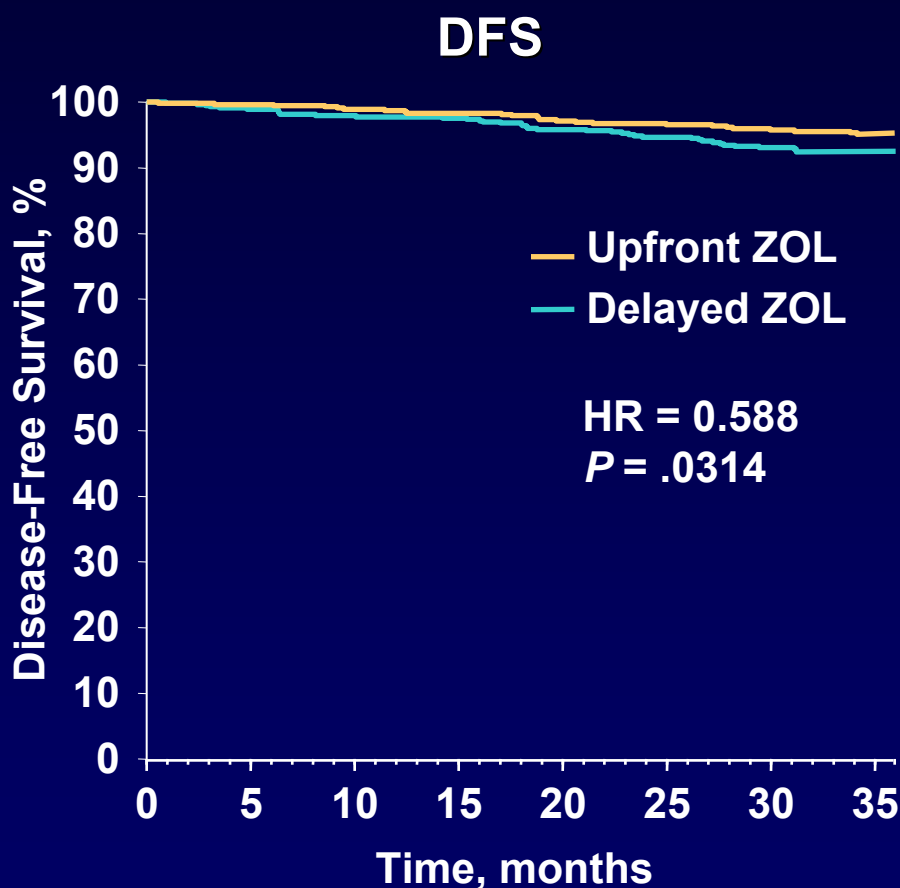
- Multicenter, open-label, randomized phase III study of upfront vs. delayed^a zoledronic acid (4 mg q 6 months) in postmenopausal women receiving letrozole (N = 1,064) for 5 years



P < .0001 for all; correspond to intergroup comparisons.
BMD, bone mineral density; ZOL, zoledronic acid.

^a Initiated only after T-score decreases below -2 or clinical fracture unrelated to trauma.

ZO-FAST 36-Month Analysis: Upfront ZOL significantly decreased the risk of DFS events by 41%



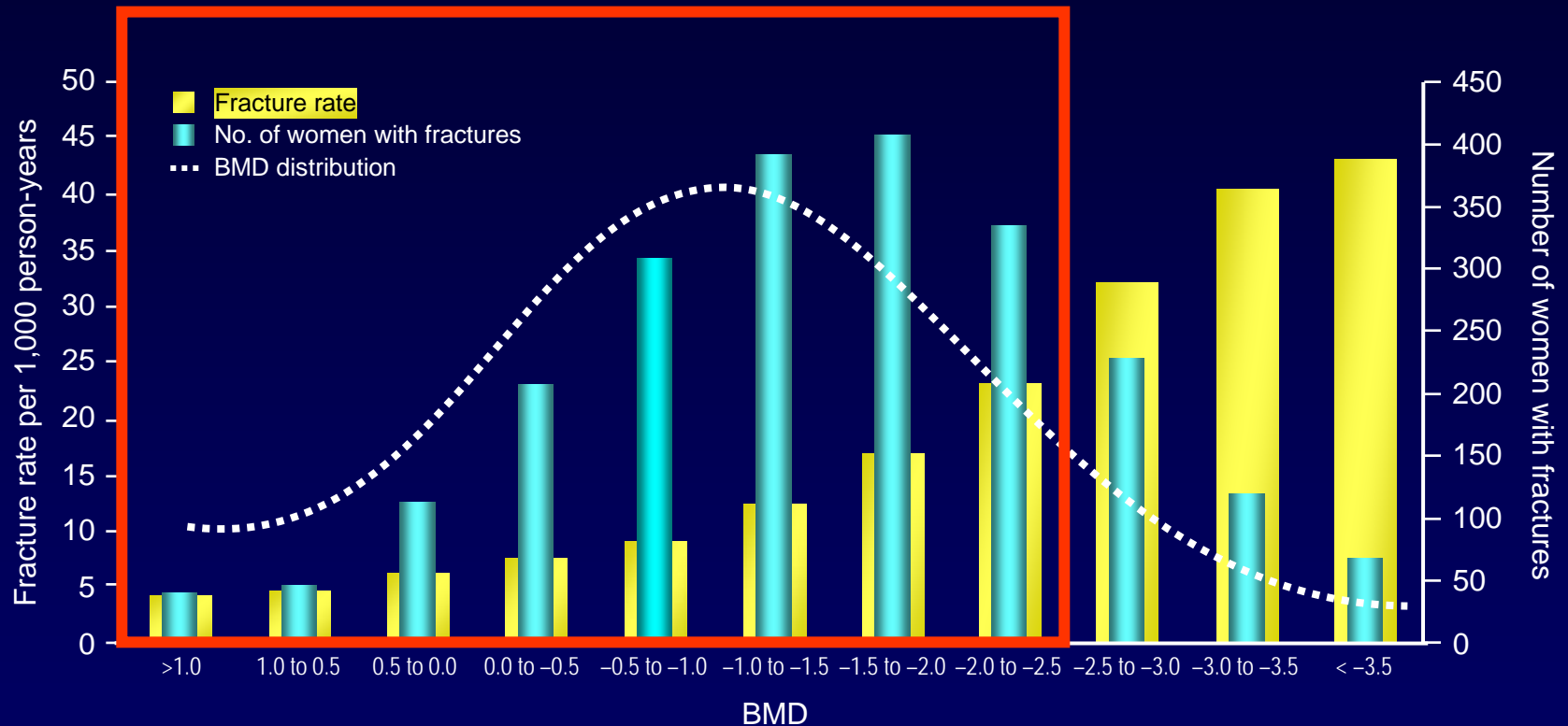
ZOL, zoledronic acid; HR, hazard ratio (Cox regression); DFS, disease-free survival.

^a Multiple sites of metastases may be reported for the same patient.

Sites of distant metastases include: bone, brain, liver, lung, skin, lymph node, and other.

Adapted from Eidtmann H, et al. SABCs 2008, Abstract #44.

80% of Fractures Occur in Women Who Are Not Osteoporotic



- Fracture rate increases ~2-fold in osteopenic women
- Majority of fractures occur in osteopenic women (T-Score -1.0 to -2.5)

Risk factors for osteoporotic fractures

- Age >75
- Previous fragility fracture above the age of 50
- Parental history of fracture
- BMI <22
- Alcohol consumption of more than 4 units per day
- Disease known to increase fracture risk eg. Crohn's
- Prior corticosteroid use for more than 6 months

Management of Bone Loss in Early Breast Cancer

(Postmenopausal Adjuvant Tx)

Commencing AI Therapy

All other pts

Age \geq 75 years and \geq 1 clinical risk factors

Measure BMD by axial DXA (spine and hip) within 3-6 mos

Low T-score $<$ -2.0 or known vertebral fracture

Low T-score $<$ -1.0 but $>$ -2.0

Both T-scores $>$ -1.0

- Assess for 2° osteoporosis
- Calcium + vit D supp if clinically deficient

- Lifestyle advice
- Calcium + vit D supp if clinically deficient

- Lifestyle advice
- Reassure pt
- No further assessment unless clinically indicated

Treat w/ bisphos at osteoporosis doses and calcium + vit D supp

Repeat axial BMD, if available, after 24 mos of therapy

Repeat axial DXA at 24 mos and/or monitor if desired with biochemical markers

Annual rate of bone loss $>$ 4% at lumbar spine or total hip and/or T-score $<$ -2.0

Yes

No

High Risk
Med Risk
Low Risk