

Case #7

Endocrine Responsive Node Negative Breast Cancer in a Premenopausal Patient: Risk Assessment and Treatment Planning

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Very Interesting Case!

1. Aim / Target of breast screening

- Non palpable / mammographically detected tumors

2. Small tumor size

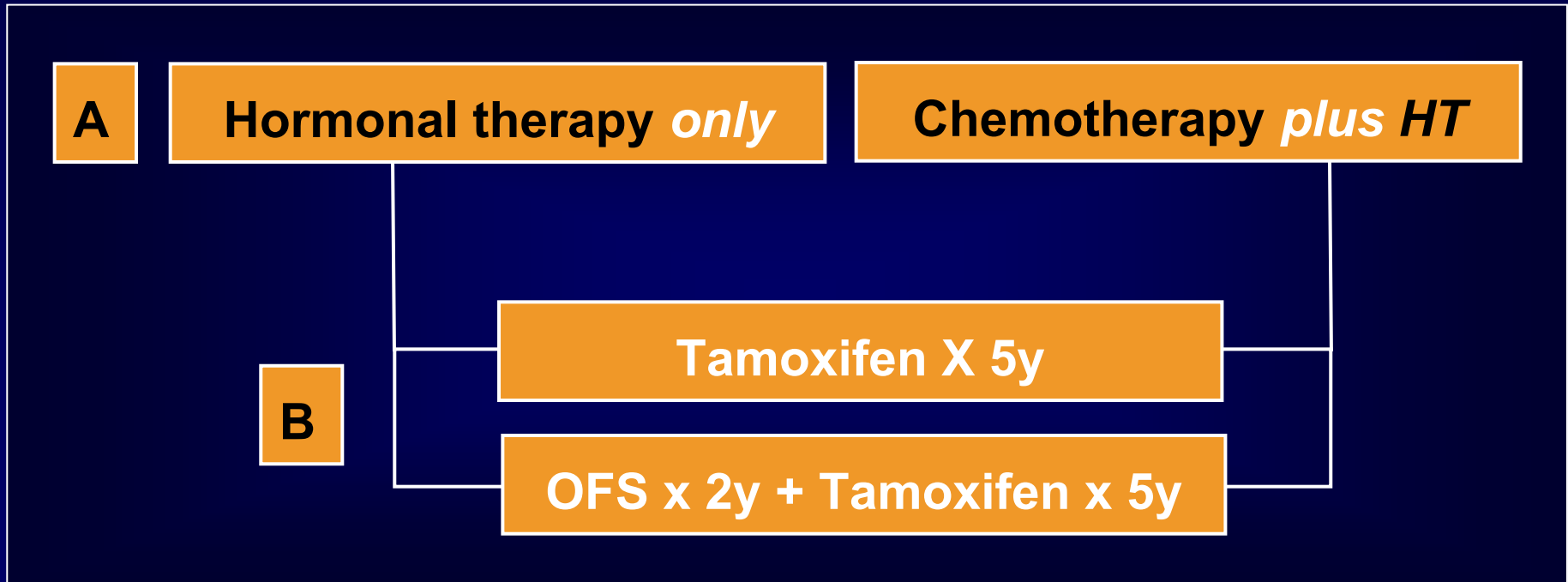
- Ideal for Breast Conserving Surgery
- Most likely with negative axillary nodes – ideal for SLNB

3. Borderline characteristics - excellent prognosis

- Difficult treatment decisions
- Insufficient data for 'modern' therapies

Part I

- Which of the following options for systemic adjuvant therapy would you recommend?



Premenopausal patients with endocrine-responsive disease

Chemotherapy to give *or* not to give?

‘Perhaps the most difficult question
in current adjuvant therapy’

- There are only underpowered clinical trial results to aid in this decision.
- Lymph node status and not endocrine responsiveness is often the primary disease characteristic to consider selection of treatment*.
- Perceived estimation of risk of relapse is the primary determinant for using ChemoT, despite of the degree of benefit it offers when added to HT.

* Regan MM et al. *Annals of Oncology*, March 5, 2008

Low risk: Node negative AND all of the following features:

Characteristic	Yes	No
pT ≤2 cm	1,1	
Grade 1		2
Absence of extensive peritumoral vascular invasion	√	
ER and PgR expressed	√	
HER2/neu gene neither overexpressed nor amplified	√	
Age ≥35 years	44	

Adjuvant therapy for hormone-sensitive breast cancer in premenopausal women

St. Gallen consensus 2003 - 2007

Risk group	Treatment
Node-negative Minimal risk	Tamoxifen OR none
Node-negative Average risk	LHRHa (or ovarian ablation) + tamoxifen OR Tamoxifen OR Chemotherapy → tamoxifen OR LHRHa (or ovarian ablation)

What Adds Chemotherapy?

Calculate for Mortality

Decision: No Additional Therapy



- 90.4 out of 100 women are alive in 10 years.
- 7.9 out of 100 women die because of cancer.
- 1.7 out of 100 women die of other causes.

With Hormonal Therapy: Benefit 2.4 alive.



With Chemotherapy: Benefit 2.3 alive.



With Combined Therapy: Benefit 4.0 alive.



1st Generation regimens - CMF, CA*4, FE(50)C*6



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With Hormonal Therapy: Benefit 2.4 alive.



With Chemotherapy: Benefit 3.4 alive.



With Combined Therapy: Benefit 4.8 alive.



2nd Generation regimens - CAF*6, FEC*6, FE(100)C*6, FAC*6, CA*4+T*4)



What Adds Chemotherapy?

Calculate for Relapse

Decision: No Additional Therapy



- 73.7 alive and without cancer in 10 years.
- 24.8 relapse.
- 1.5 die of other causes.

With Hormonal Therapy: Benefit 9.0 without relapse.



With Chemotherapy: Benefit 8.3 without relapse.



With Combined Therapy: Benefit 14.4 without relapse.



1st Generation regimens - CMF, CA*4, FE(50)C*6



What Adds Chemotherapy?

Calculate for Relapse

Decision: No Additional Therapy



■ 73.7 alive and without cancer in 10 years.

■ 24.8 relapse.

■ 1.5 die of other causes.

With Hormonal Therapy: Benefit 9.0 without relapse.



With Chemotherapy: Benefit 11.4 without relapse.



With Combined Therapy: Benefit 16.4 without relapse.



2nd Generation regimens - CAF*6, FEC*6, FE(100)C*6, FAC*6, CA*4+T*4)



Oncotype DX[®]

- a 21-gene recurrence score (RS) assay
- The Recurrence Score[™] (RS) result quantifies the risk of recurrence in women with N-, ER+ breast cancer and also predicts the magnitude of chemotherapy benefit (predictive)
- **Patients with a low RS have minimal, if any benefit, from chemotherapy while patients with a high RS have a significant benefit from chemotherapy**

Oncotype DX™ 21-Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION

Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN

ER
PR
Bcl2
SCUBE2

$$\begin{aligned}
 \text{RS} = & + 0.47 \times \text{HER2 Group Score} \\
 & - 0.34 \times \text{ER Group Score} \\
 & + 1.04 \times \text{Proliferation Group Score} \\
 & + 0.10 \times \text{Invasion Group Score} \\
 & + 0.05 \times \text{CD68} \\
 & - 0.08 \times \text{GSTM1} \\
 & - 0.07 \times \text{BAG1}
 \end{aligned}$$

GSTM1

BAG1

INVASION

Stromelysin 3
Cathepsin L2

CD68

REFERENCE

Beta-actin
GAPDH
RPLPO
GUS
TFRC

HER2

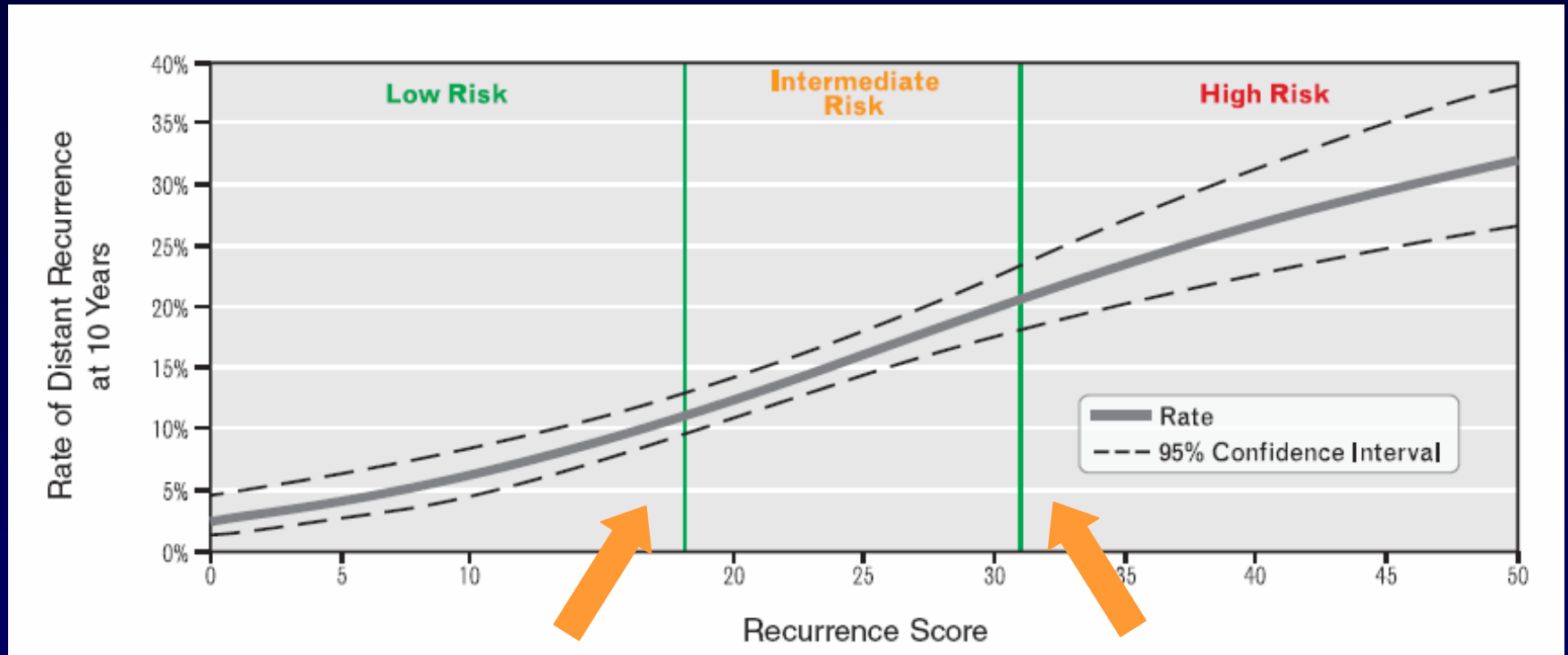
GRB7
HER2

Category	RS (0-100)
Low risk	RS <18
Interm risk	RS ≥18 and <31
High risk	RS ≥31

*Paik et al. *N Engl J Med.* 2004;351:2817-2826.

Onco^{type} DX[®] is a Standardized and Quantitative Assay

Recurrence Score in N-, ER+ patients



Lower RS's

- Lower likelihood of recurrence
- Minimal, if any, chemotherapy benefit

Higher RS's

- Greater likelihood of recurrence
- Clear chemotherapy benefit

1) Paik et al. *NEJM* 2004, 2) Habel et al. *Breast Cancer Research* 2006

3) Paik et al. *JCO* 2006, 4) Gianni et al. *JCO* 2005

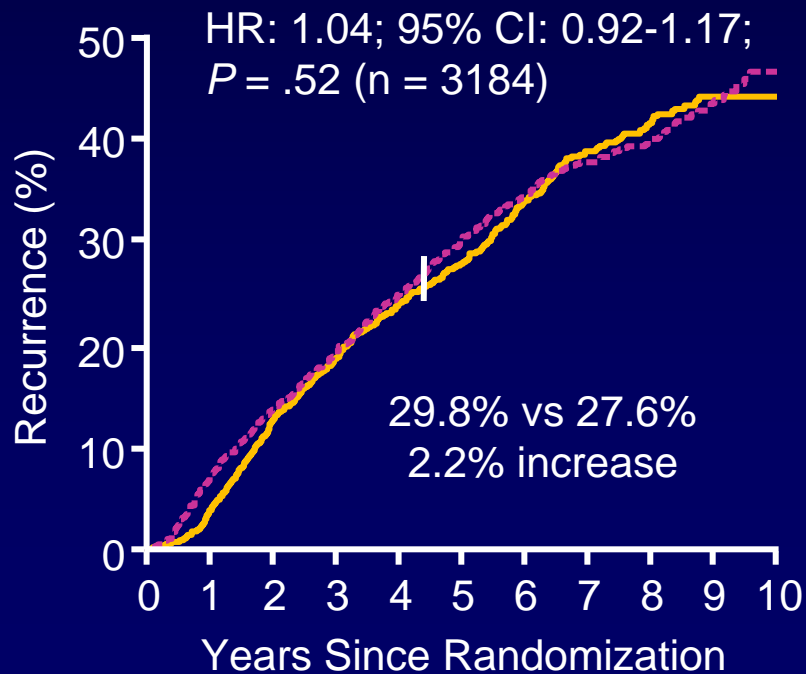
Role of Endocrine Therapy

- **Options include:**
 - **Tamoxifen alone**
 - **Tamoxifen combined with ovarian ablation *via***
 - **LHRHa therapy** (*recommended*)
 - **Oophorectomy** (*accepted as a reasonable alternative*)
 - **Radiotherapy** (*not acceptable*)
 - **Ovarian ablation *and* Aromatase inhibitors?**

LHRH Agonist Therapy as Effective as Chemotherapy

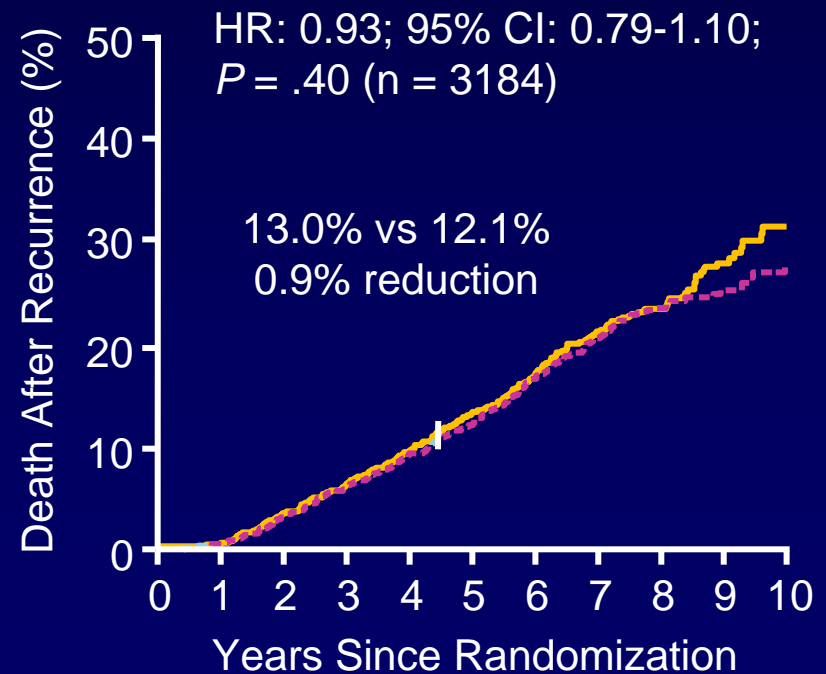
Recurrence

- Chemotherapy
- - LHRH agonist

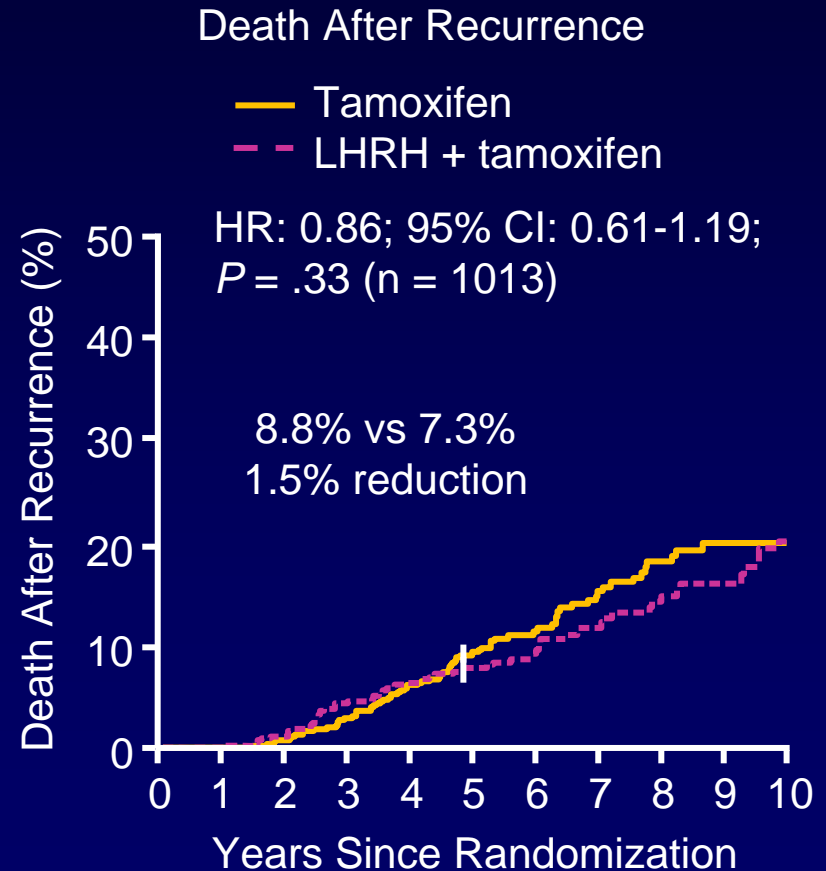
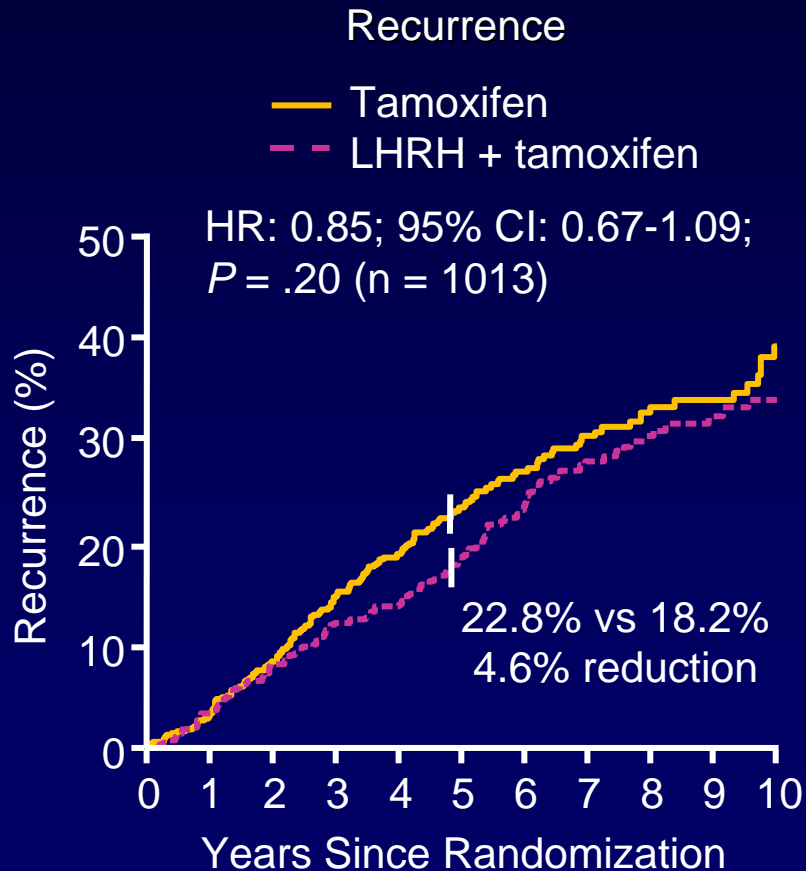


Death After Recurrence

- Chemotherapy
- - LHRH agonist



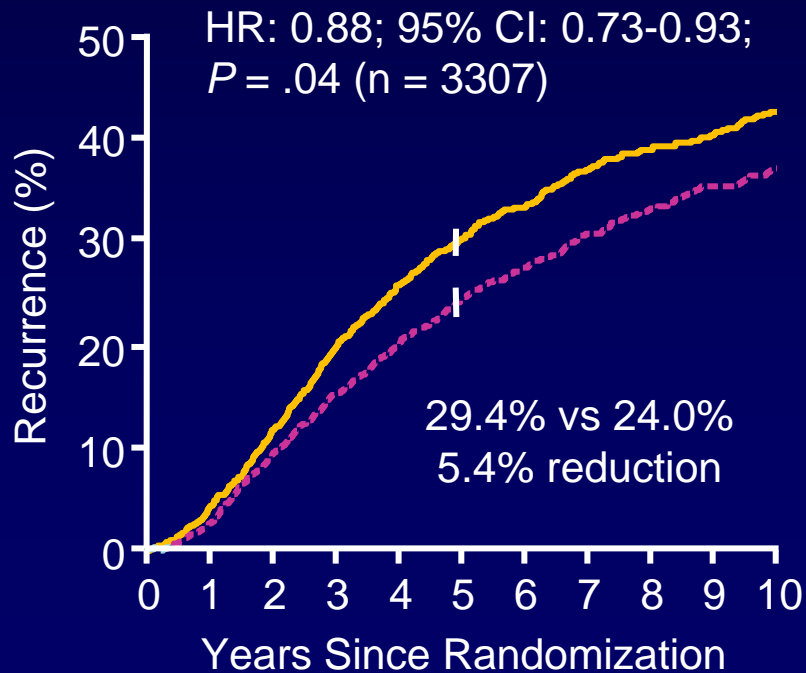
Small Clinical Benefit of Adding LHRH Agonist to Tamoxifen



Some Clinical Benefit of Adding LHRH Agonist to Chemotherapy

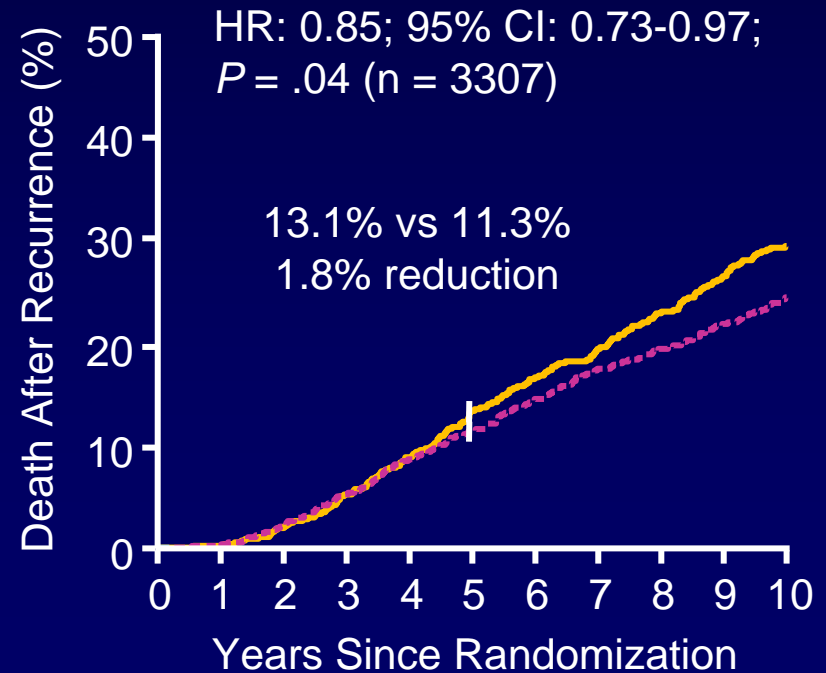
Recurrence

- Chemotherapy ± tamoxifen
- - LHRH addition



Death After Recurrence

- Chemotherapy ± tamoxifen
- - LHRH addition



LHRH-Agonists in HR+ Early BC

- **Adjuvant LHRHa is effective in premenopausal women with HR-positive early breast cancer**
 - As effective as chemotherapy (*mainly CMF*)
 - Some benefit when used with tamoxifen
 - An additional benefit when used with chemotherapy \pm tamoxifen only in women younger than 40 years of age
 - More favorable side-effect profile compared with chemotherapy
- **LHRHa and Aromatase inhibitors?**

Pre-menopausal, ER+: trials with AIs

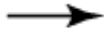
Study	Design	Patient Population	Questions
SOFT (IBCSG 24-02)	TAM 5 y vs TAM 5 y + OS vs EXE 5 y + OS	2,700 pre-menopausal women with endocrine responsive disease treated with no adjuvant chemo or remain pre-menopausal after chemotherapy	- Does OS add to TAM (or EXE) in pre-menopausal women not treated with chemotherapy? - Does OS add to chemo in pre-menopausal women?
TEXT (IBCSG 25-02)	OS + TAM 5 y vs OS + EXE 5 y	2,025 pre-menopausal women with endocrine responsive disease and candidates for OFS, and who may or not receive chemotherapy	Is an AI superior to TAM in pre-menopausal women treated with OS?
ABCSG 12	OS + TAM vs OS + Anastrozole	1,750 pre-menopausal women with endocrine responsive disease	Is an AI superior to TAM in pre-menopausal women treated with OS?

SOFT: Suppression of Ovarian Function Trial

TEXT: Tamoxifen and Exemestane Trial

A: IBCSG Trial 11-93

Primary Surgery for ER and /or PgR +, node positive breast cancer



Stratify

- Institution
- Local treatment
- OFS plan (1)

Random Assignment



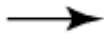
OFS + Tamoxifen x 5 yrs



AC chemotherapy + OFS + Tamoxifen x 5 yrs

B: PERCHE (IBCSG Trial 26-02)

Primary Surgery for ER and /or PgR +, breast cancer



Stratify

- Institution
- Nodal status
- OFS plan (2)
- CT plan (3)
- oral ET plan (4)

Random Assignment



OFS + Tamoxifen or Exemestane x 5 yrs



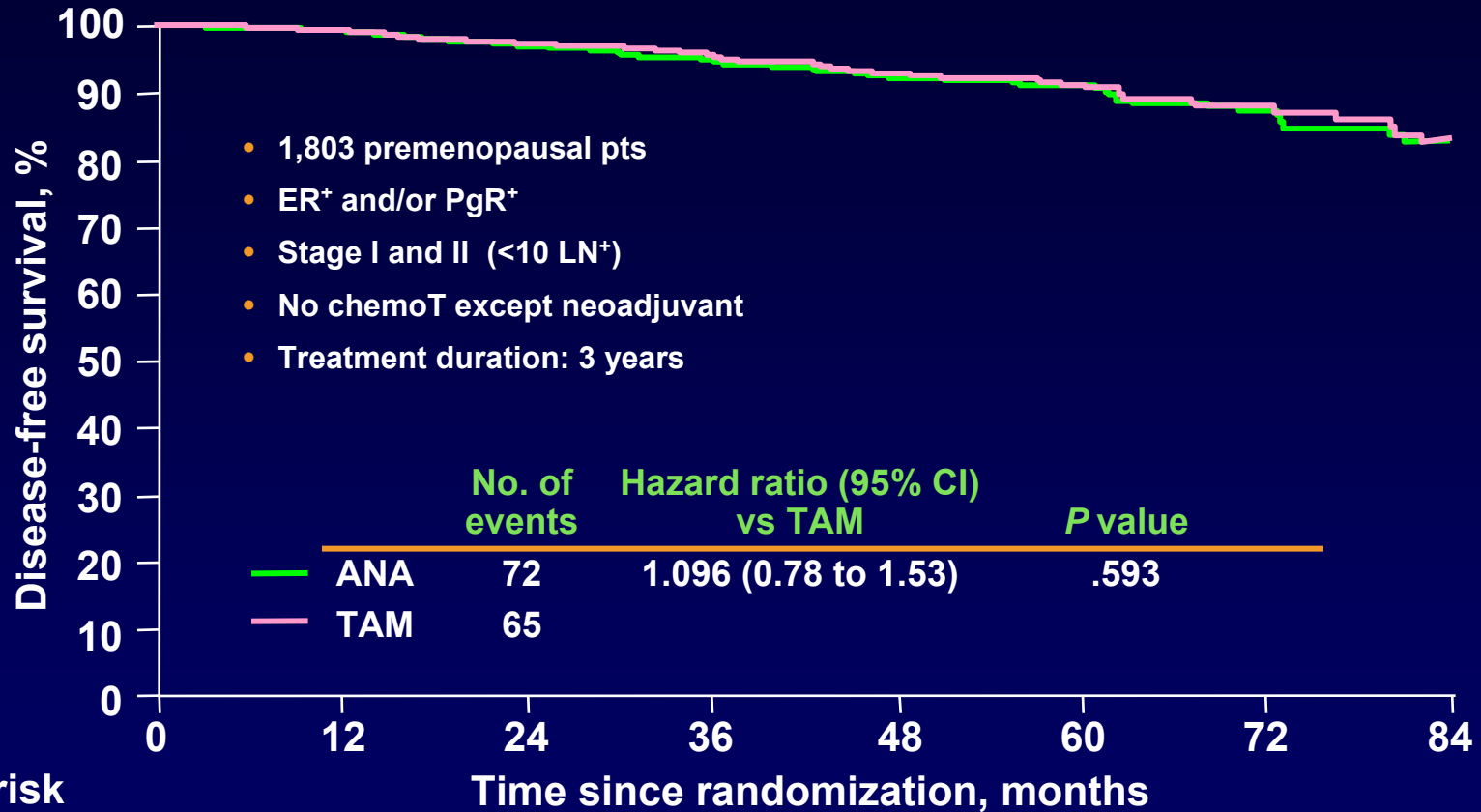
Chemotherapy + OFS + Tamoxifen or Exemestane x 5 yrs

PERCHE: Premenopausal Endocrine Responsive Chemotherapy Trial*

PROMISE: Premenopausal Optimal Management IS Endocrine therapy Trial*

*closed early due to poor accrual

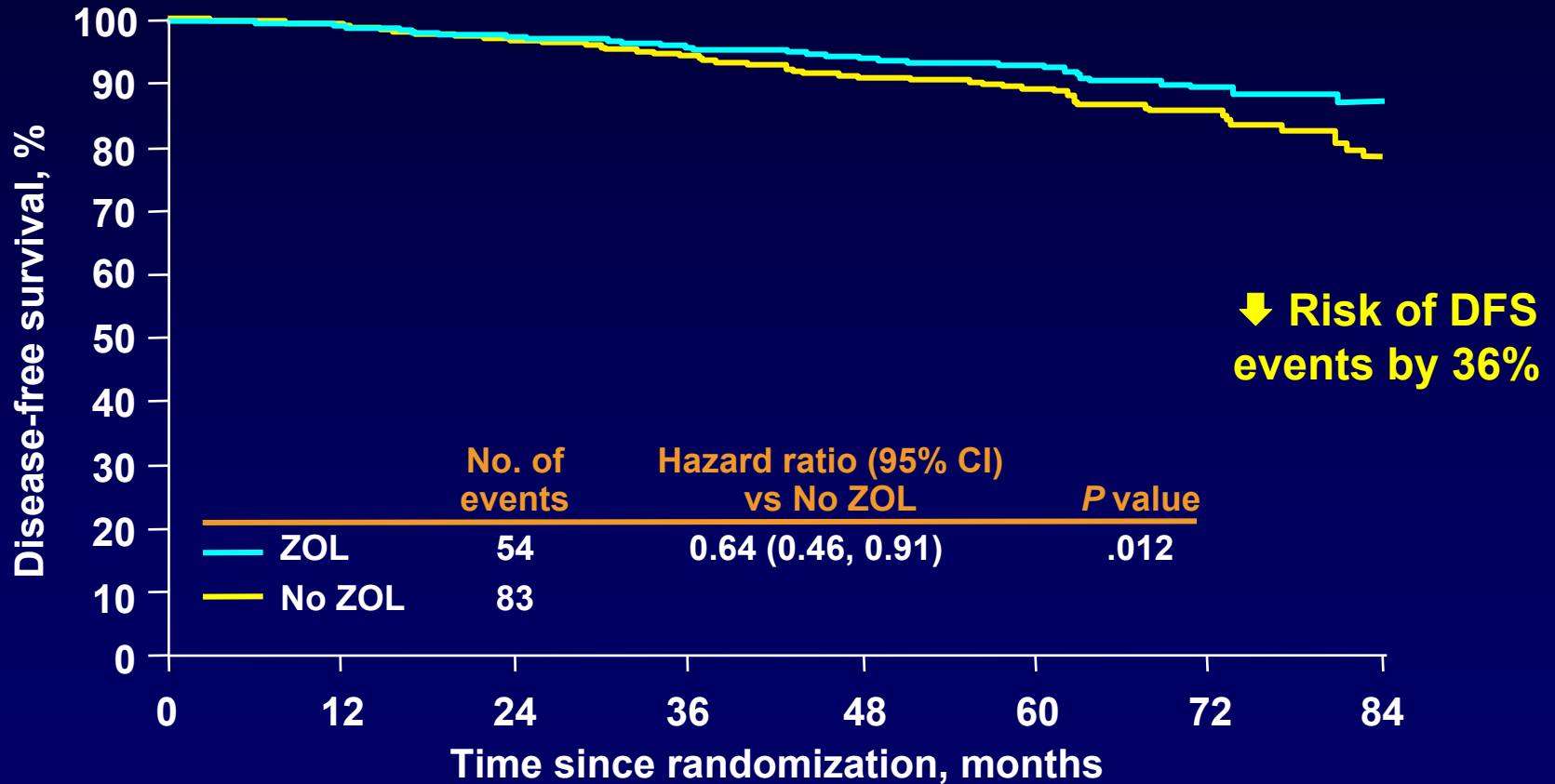
ABCSG-12: Anastrozole Does Not Improve DFS vs Tamoxifen



TAM	900	834	718	552	411	243	129	50
ANA	903	844	725	540	411	255	139	51

Median follow-up = 48 months.

ABCESG-12: ZOL Significantly Improves DFS Compared with Endocrine Therapy Alone



No. at risk

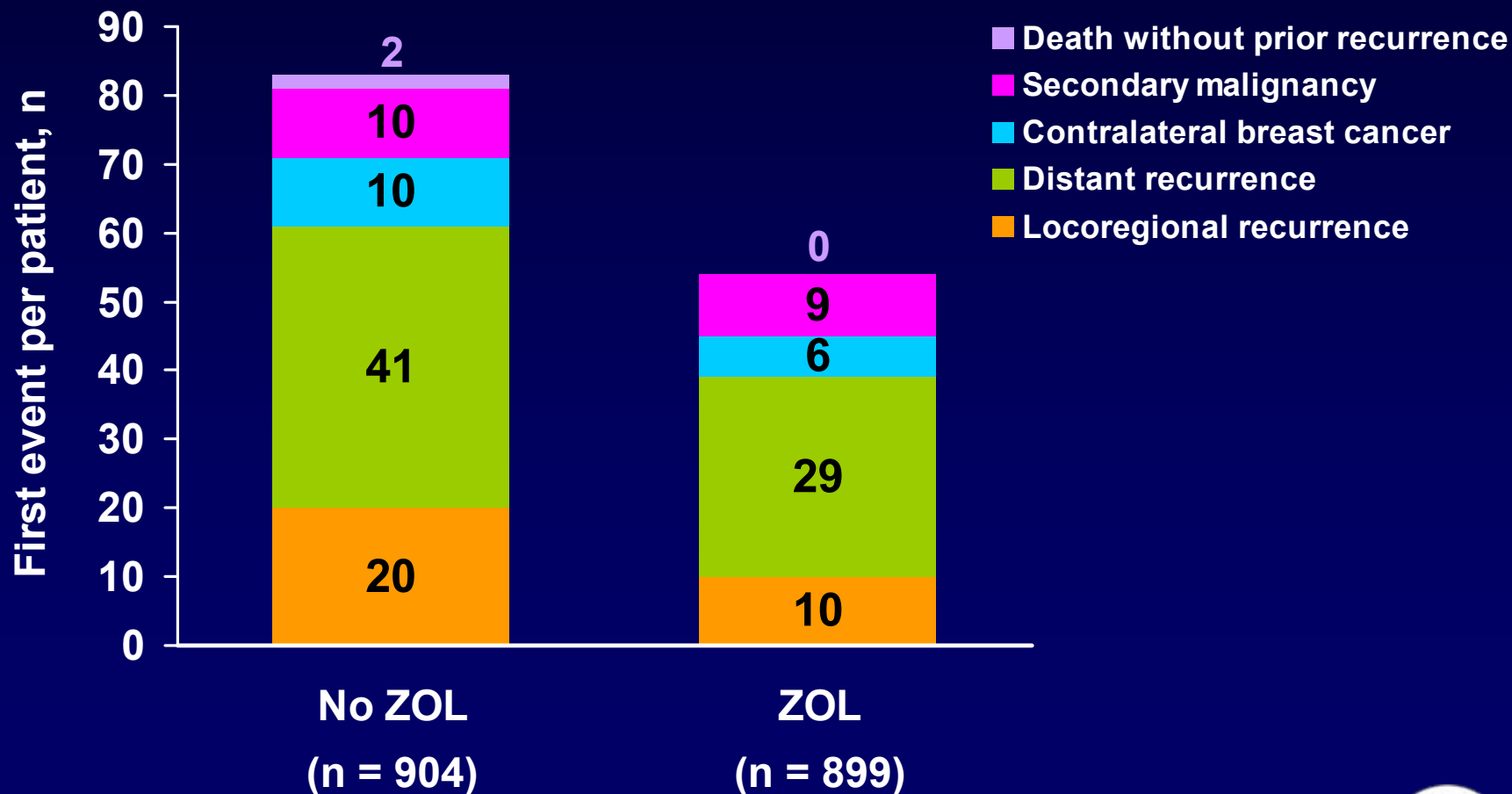
No ZOL	904	832	713	537	407	241	145	47
ZOL	899	846	730	555	414	257	123	54

Median follow-up = 48 months.

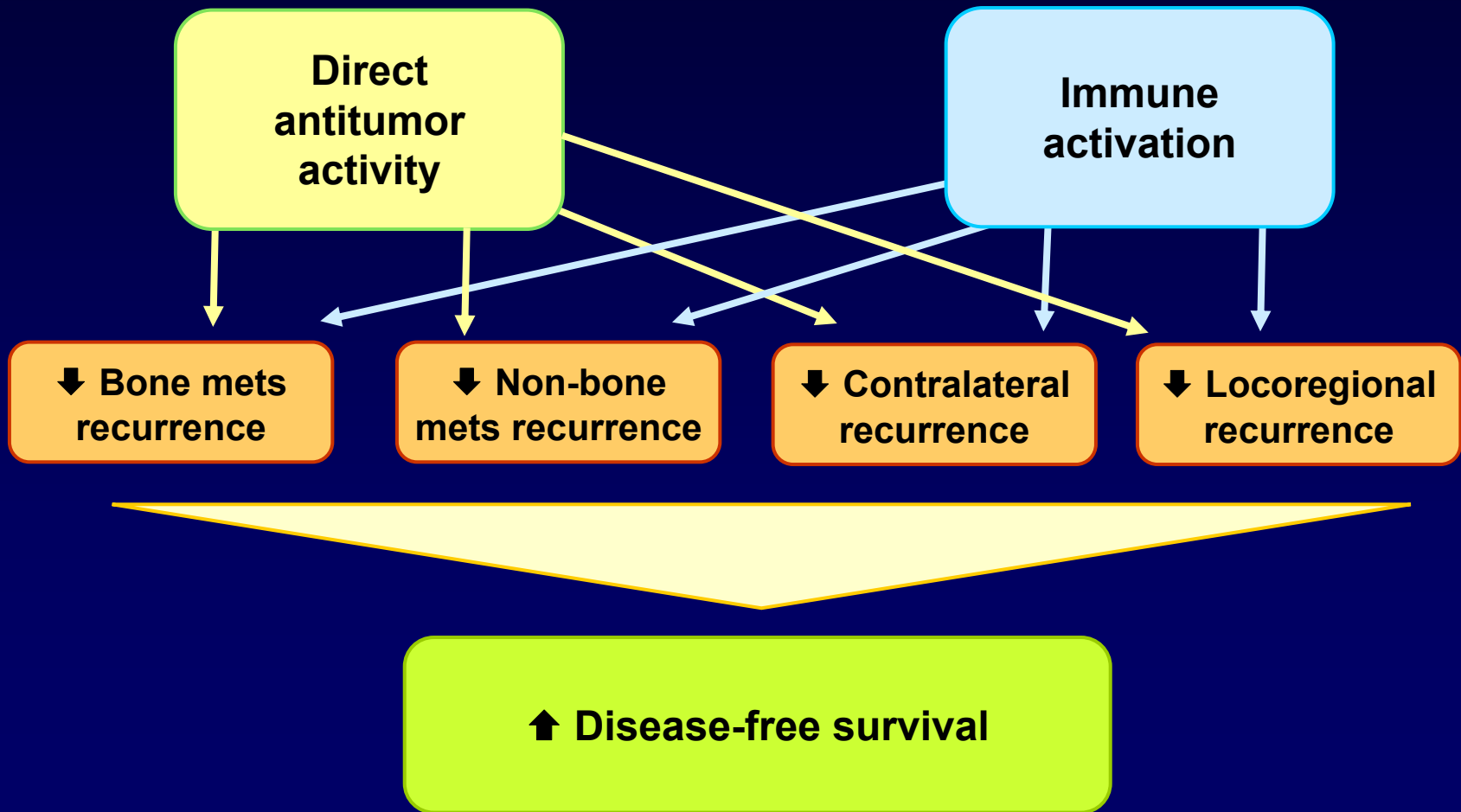
Gnant M, et al. Lancet Oncol. 2008 Sep;9(9):840-9.

ZOL Reduced Recurrence at All Sites

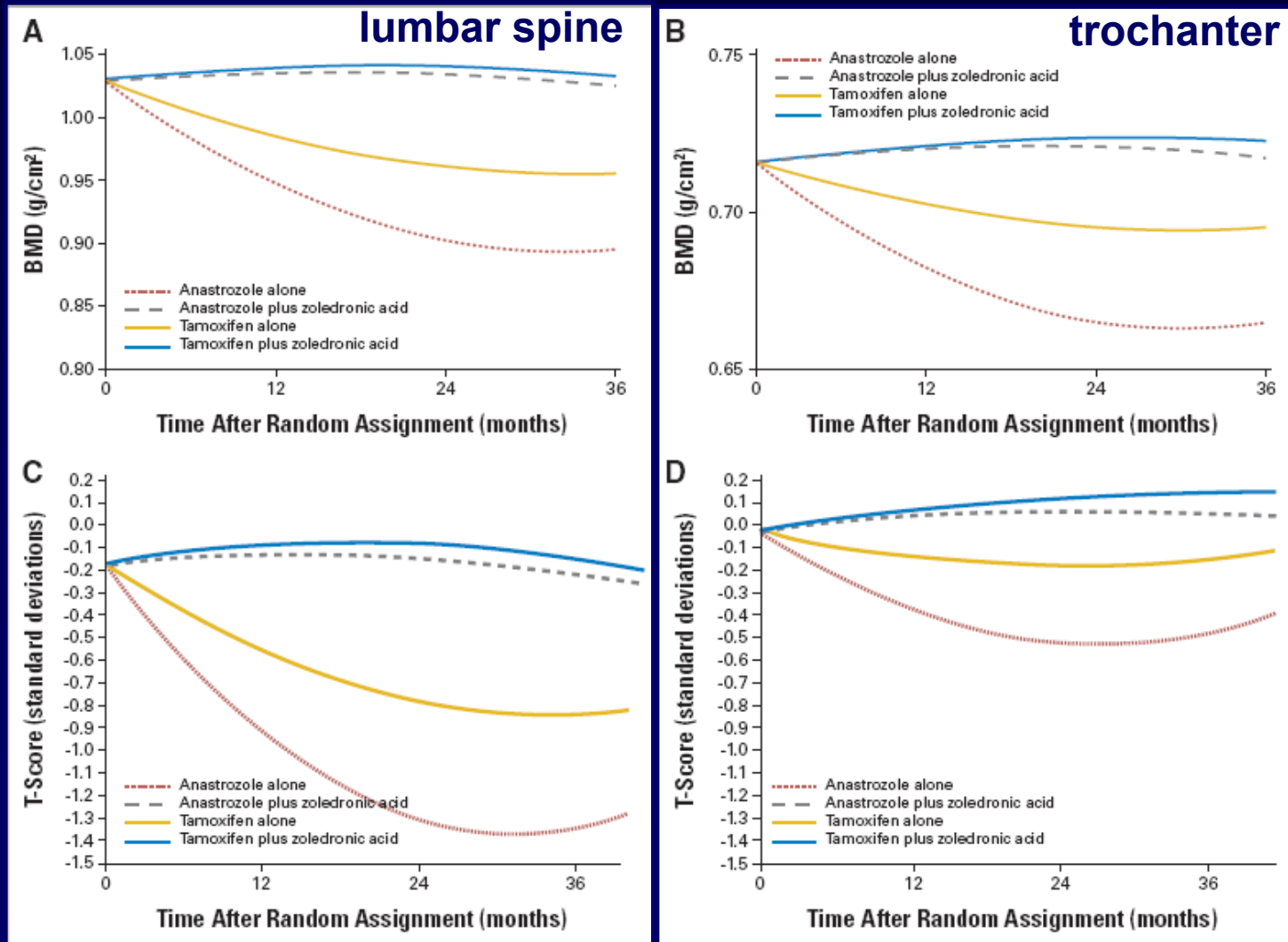
No ZOL vs ZOL



Zoledronic Acid-Mediated Mechanisms Contributing to Improved Disease-Free Survival



ZA Prevents Cancer Treatment–Induced Bone Loss in Premenopausal Women on Adj Horm Therapy



Case Summary

- **LHRHa ± tamoxifen is a standard of care in premenopausal patients with HR+ disease**
 - LHRHa + AI holds further promise, but additional data from ongoing studies (SOFT, TEXT) are awaited
- **Benefits from the addition of zoledronic acid extended beyond bone health and improved BC disease outcomes (DFS, RFS, OS)**
- **Adjuvant treatment in the premenopausal setting needs to be tailored to each patient taking into account: (1) HR status (2) there are some patients with low risk of relapse and not all premenopausal patients need adjuvant chemotherapy and (3) well informed (*SE/benefit*) patient's decision**