

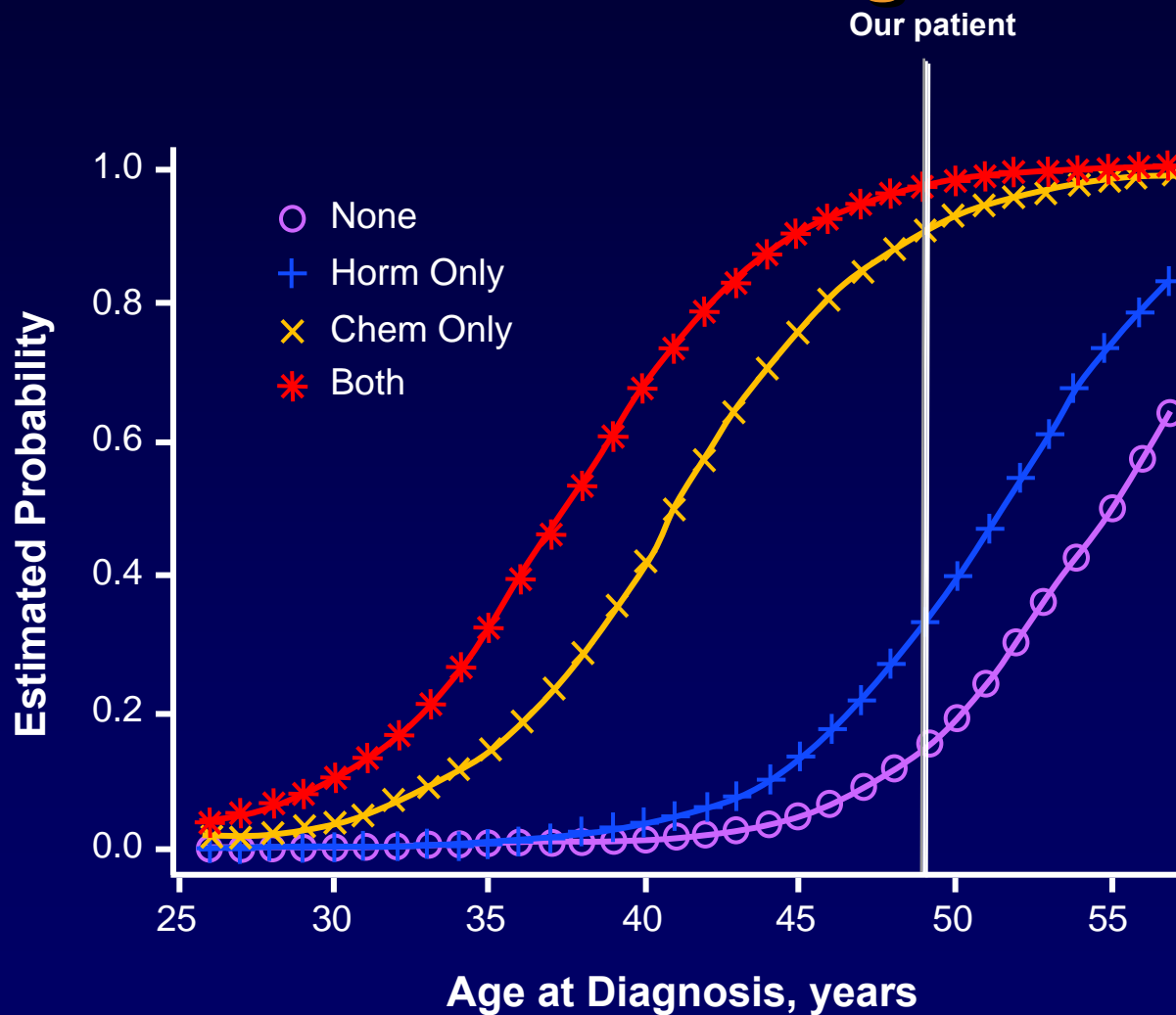
Case #3—Perimenopausal Breast Cancer: What Is the Optimal Management?

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Rates of Chemotherapy-Induced Amenorrhea

Agents	“Younger” Women (≤ 40 yr)	“Older” Women (> 40 yr)
Alkylating	18% to 61%	61% to 97%
Anthracyclines	~ 32%	~ 88%
Taxanes (+A)	~ 61%	~ 84%

Mathematical Model of Risk of Menopause: First Year After Diagnosis



Our Patient?

**Probably suitable for aromatase
inhibitor (AI) therapy**

BUT!!!

Use of AIs in Perimenopause: Royal Marsden Experience A Cautionary Tale

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), E₂, beta inhibin reflects function only at that time point, but is not predictive**
- **Tests used for E₂ measurements are unreliable in perimenopause**
- **Measurement in patients receiving a steroidal AI cross-react even with most specialized immunoassays**

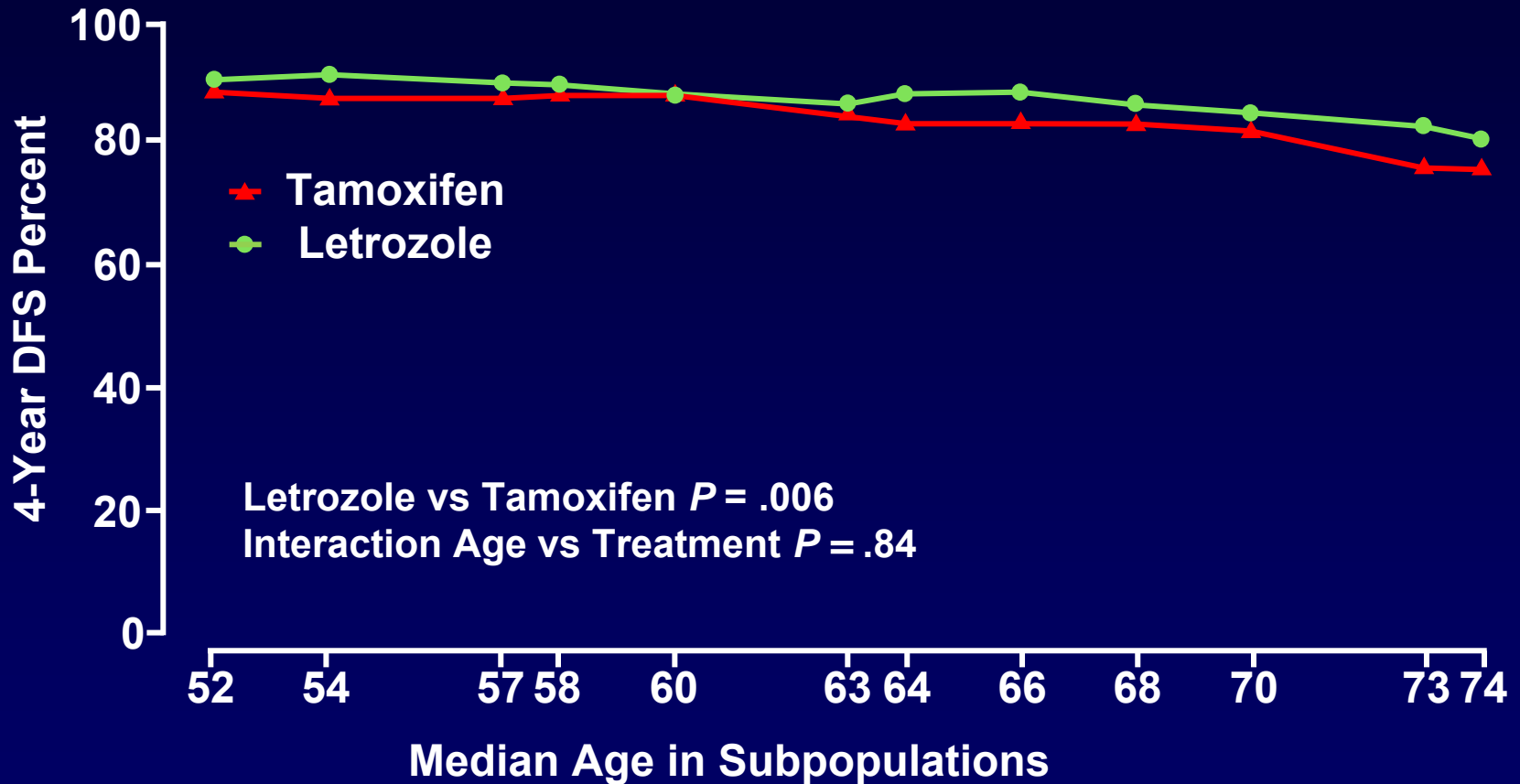
FSH = follicle-stimulating hormone; LH = luteinizing hormone

If Use of AIs Is Considered in Chemotherapy-Induced Menopause in Premenopausal or Perimenopausal Patients:

- Instruct patients to contact clinician if menstrual bleed recurs or hot flushes stop abruptly
- Serial monthly measurement of FSH and E₂
 - For at least 6 months
 - For AI after tamoxifen requires possibly even longer monitoring
- If E₂ remains >10 pmol/L = AI is not fully effective
 - Evaluate compliance
 - Consider a switch back to tamoxifen
 - Consider surgical ovarian ablation or suppression
- Adequate contraception should be practiced during monitoring period
- Anti Müllerian hormone (AMH) is most reliable indicator of residual follicular function

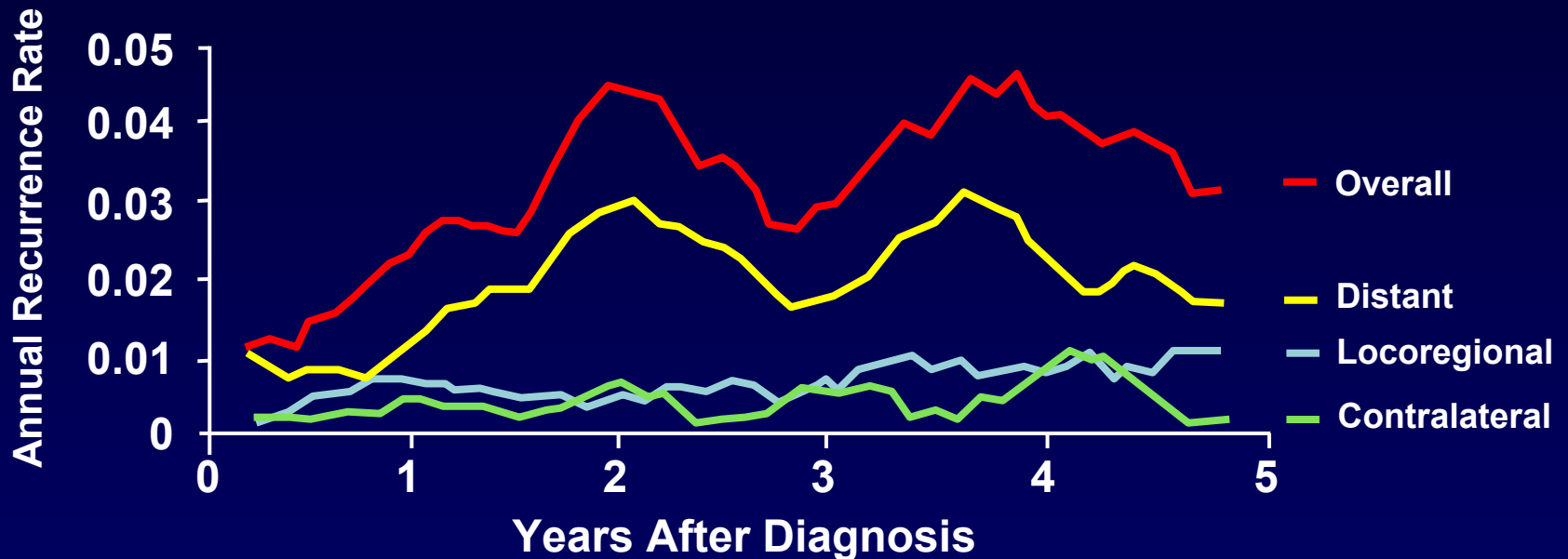
**This Can Be Done But Does It
Need to Be?**

BIG 1-98 Letrozole vs Tamoxifen STEPP* Analysis 4-Year DFS



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

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, tumor size, grade, node status, LVI all predict for early recurrence

Results

Predictors of Early vs Late Recurrence

Increasing age

Tumor size

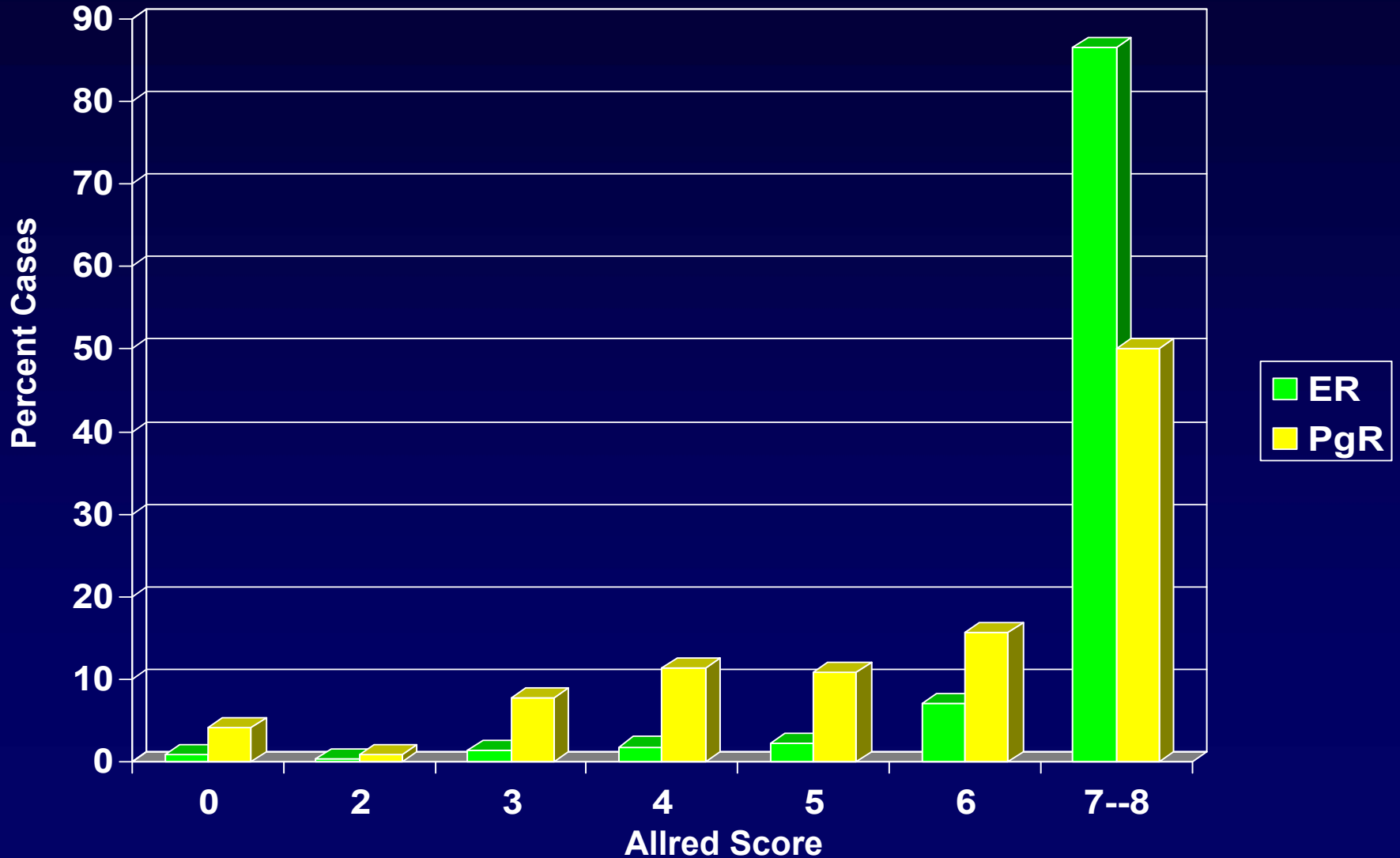
Predictors for Early Relapse AI vs Tamoxifen (BIG 1-98)

- **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

**Can We Use High Precision
Quantitative ER and PGR to
Refine Prediction of
Early Relapse?**

TEAM Pathology: Estrogen Receptor & Progesterone Receptor Allred Score Distribution

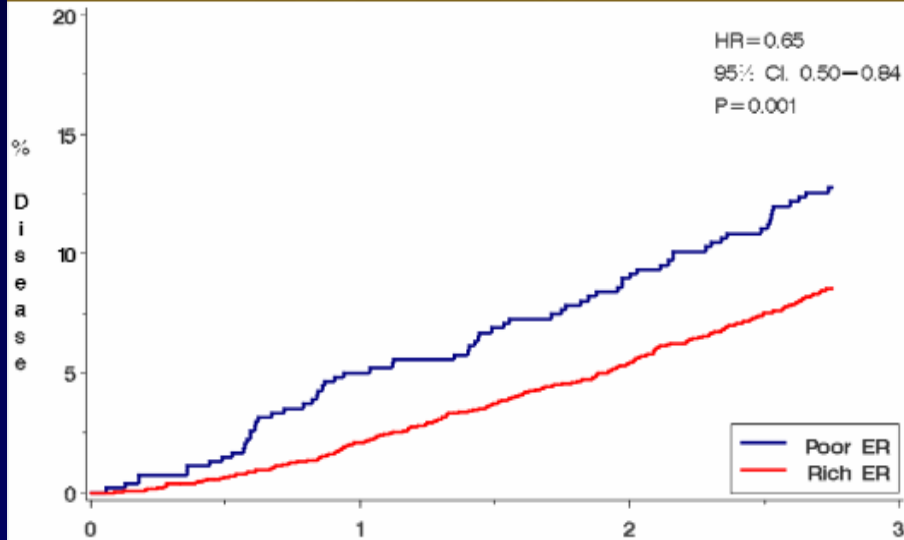


ER and PgR as a Prognostic Markers



ER as a prognostic marker in TEAM

Rich versus Poor (Allred ≤ 6 versus >6)

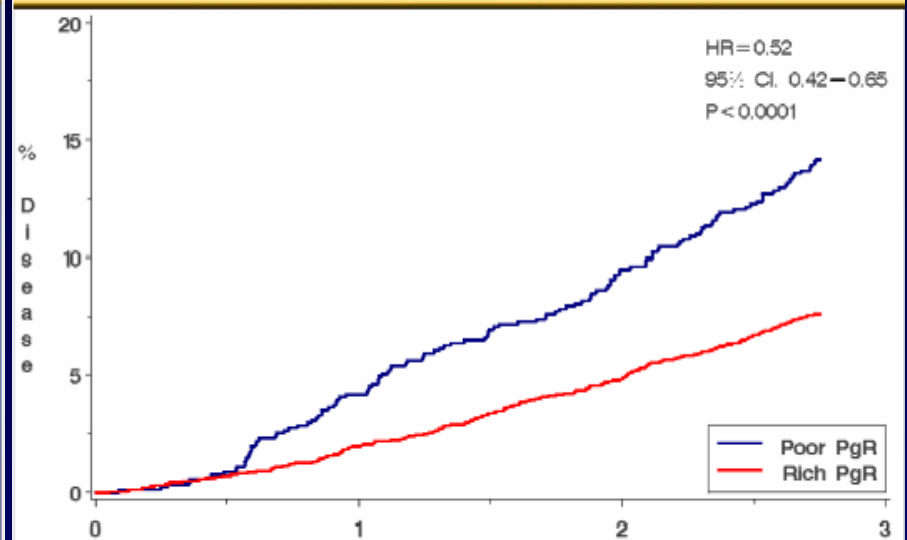


No. at Risk:		Years from Randomisation			
		0	1	2	3
Low:	538	508	483	452	452
High:	3510	3409	3220	2738	2738



PgR as a prognostic marker in TEAM

Allred ≤ 4 vs >4 .

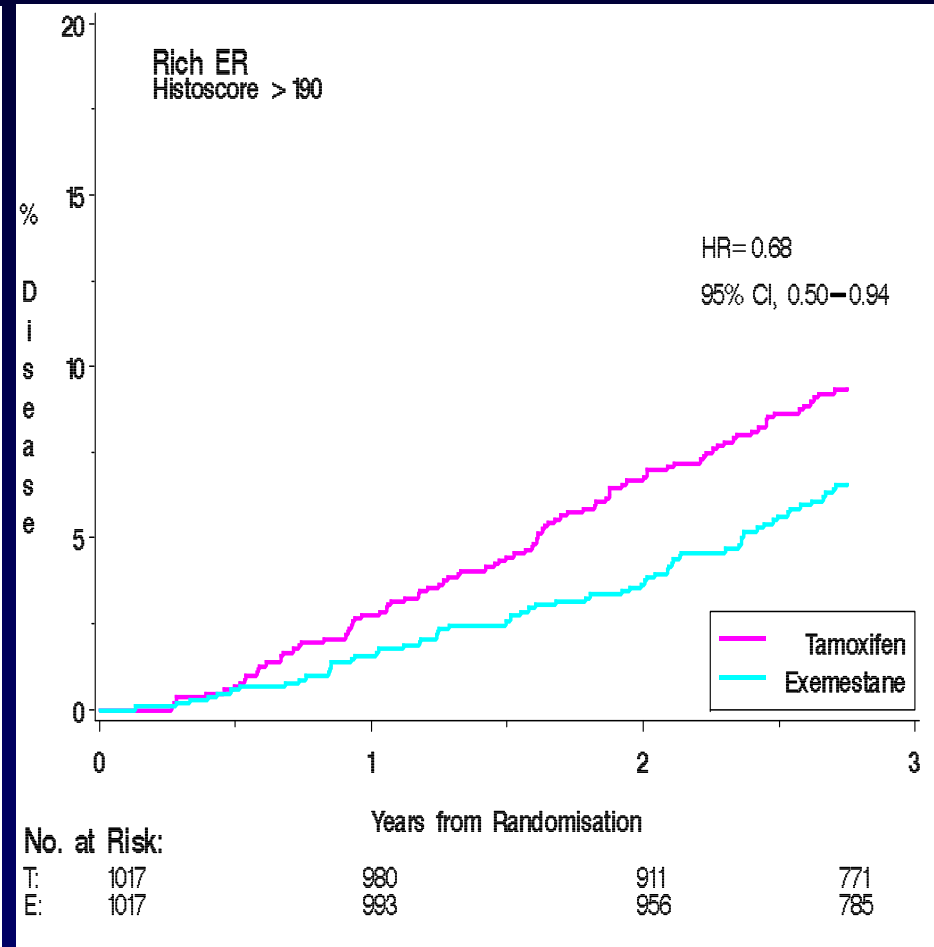
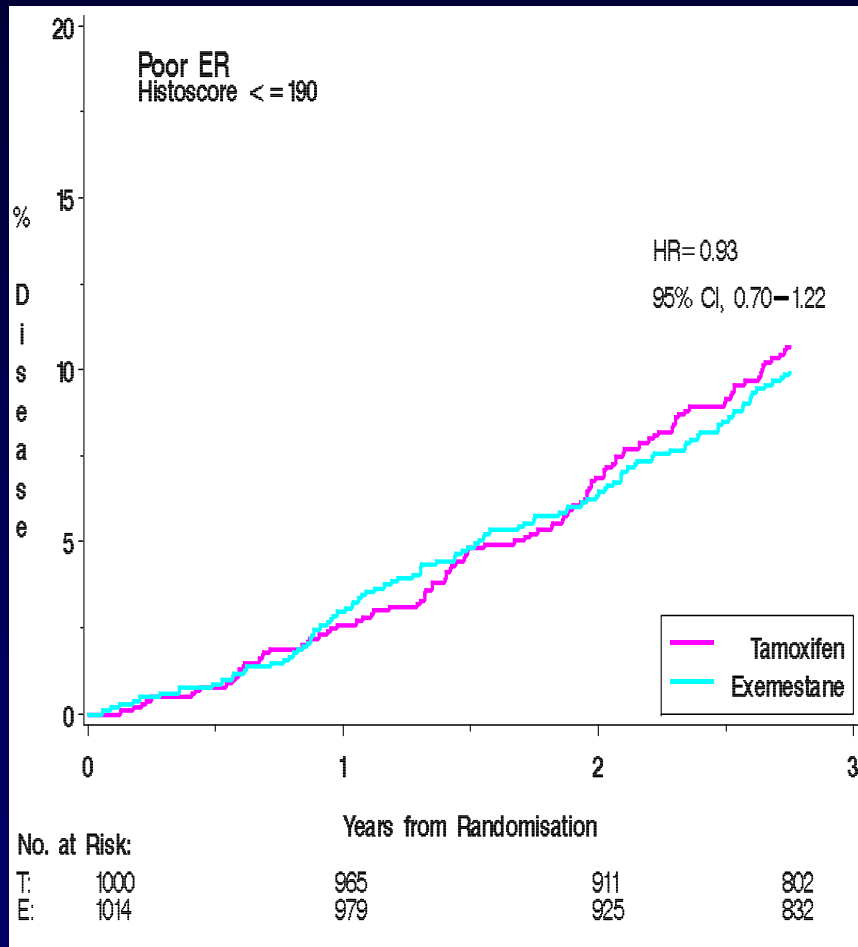


No. at Risk:		Years from Randomisation			
		0	1	2	3
Low:	911	865	805	698	698
High:	3137	3050	2696	2490	2490

ER as Predictive Marker

Exemestane versus Tamoxifen

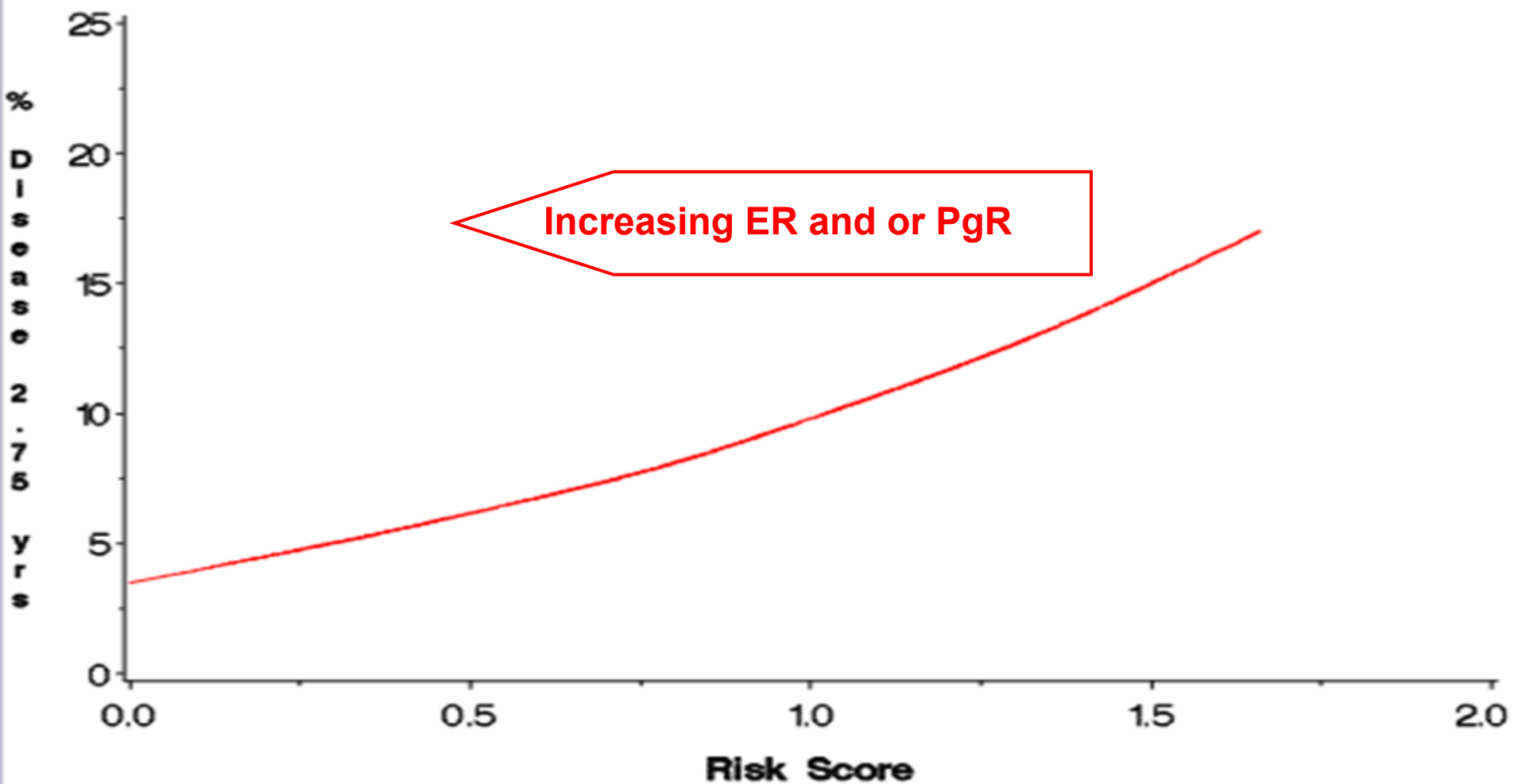
Histocore (poor ≤ 190 , Rich > 190)



- Interaction $P = .15$ (unadjusted) $P = .20$ (adjusted)

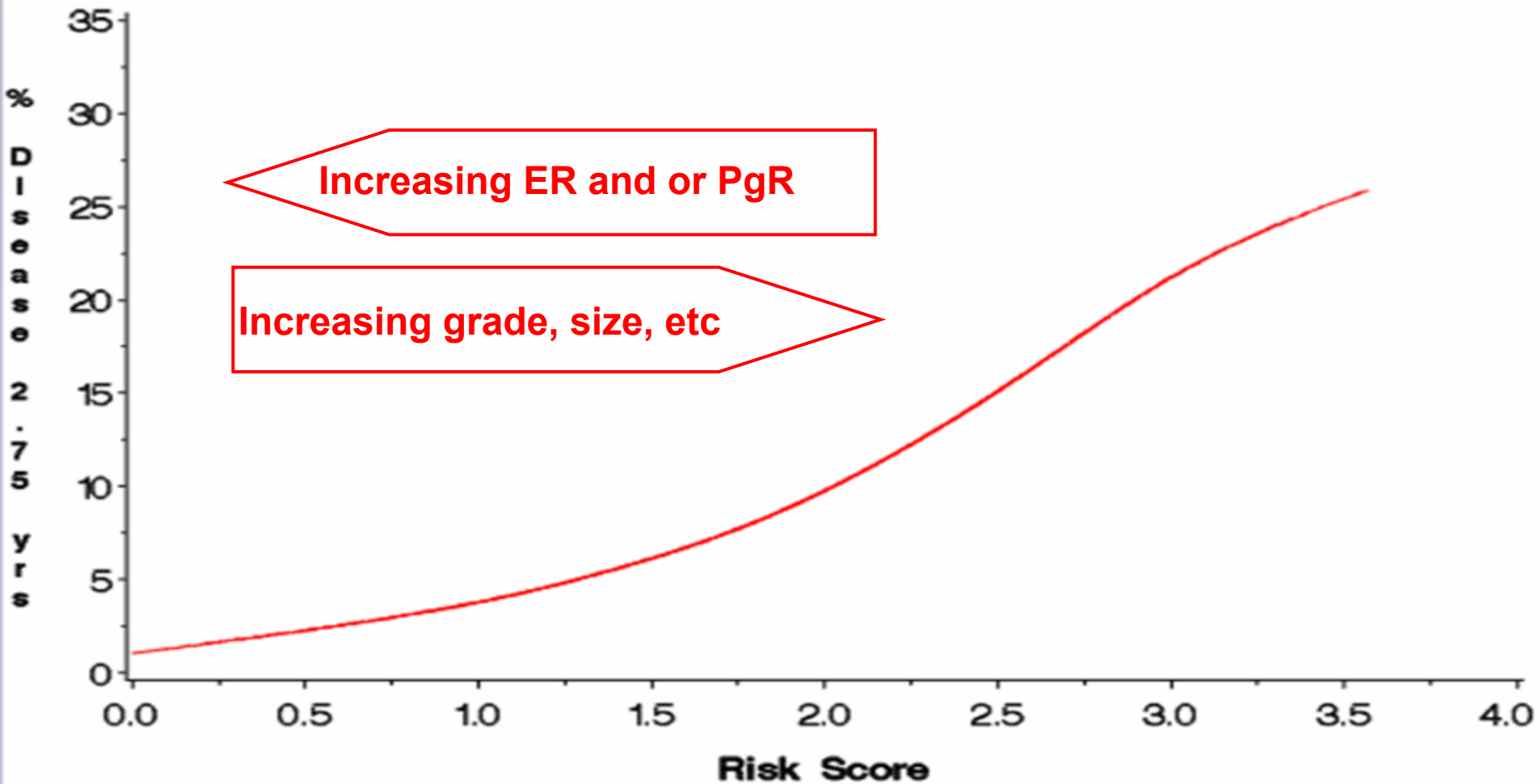
Bartlett JM, et al. *Cancer Res.* 2009;69(Suppl 2): Abstract 81.

Relapse Risk and Quantitative ER/PgR: Integrated Risk with Both HRs

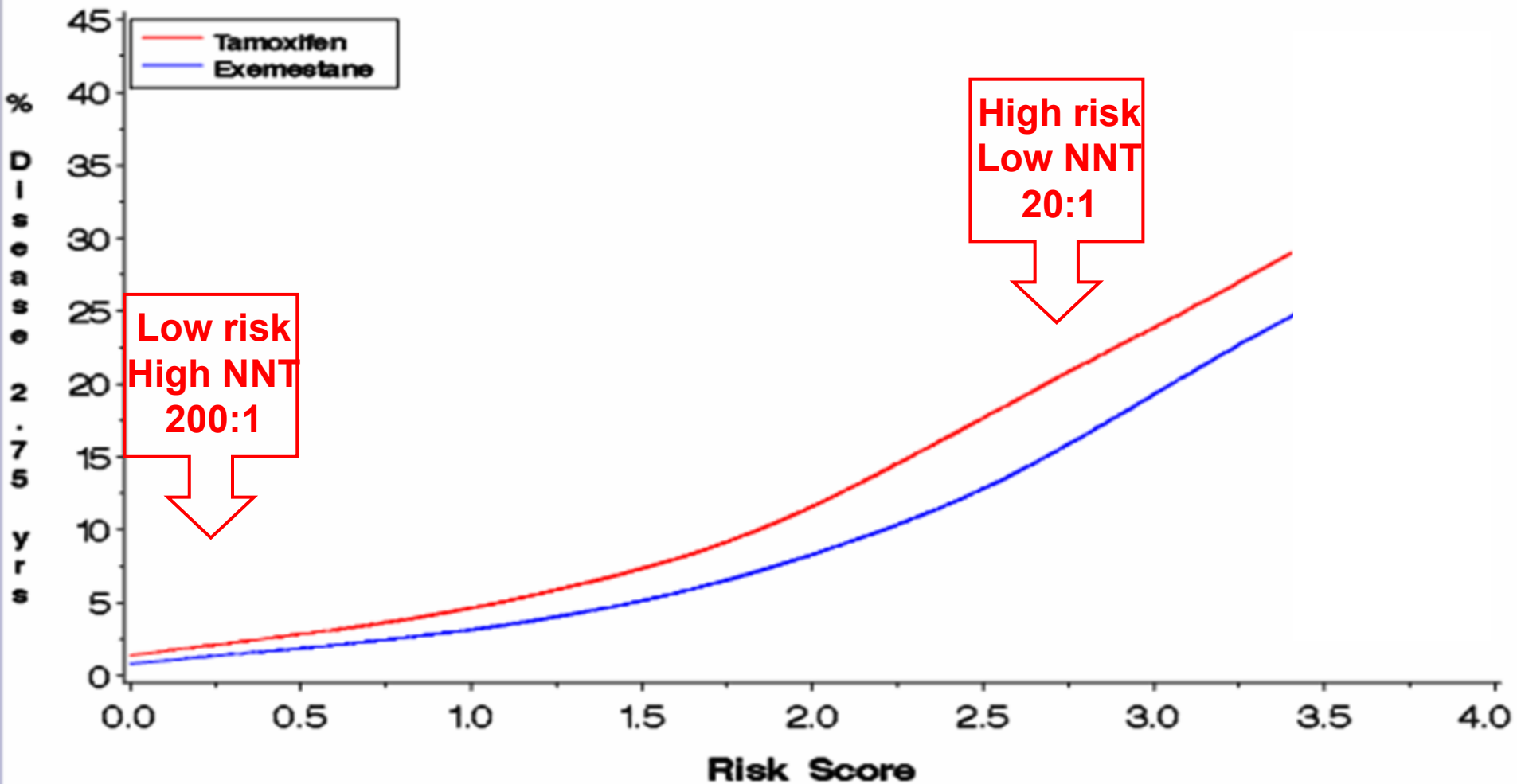


Bartlett JM, et al. *Cancer Res.* 2009;69(Suppl 2): Abstract 81.

Overall Risk of Early Relapse: ER/PgR, Nodes, Size, Grade, and Age



Overall Relapse Risk by Treatment Arm:



Pragmatic Approach to Chemotherapy Induced Amenorrhoea

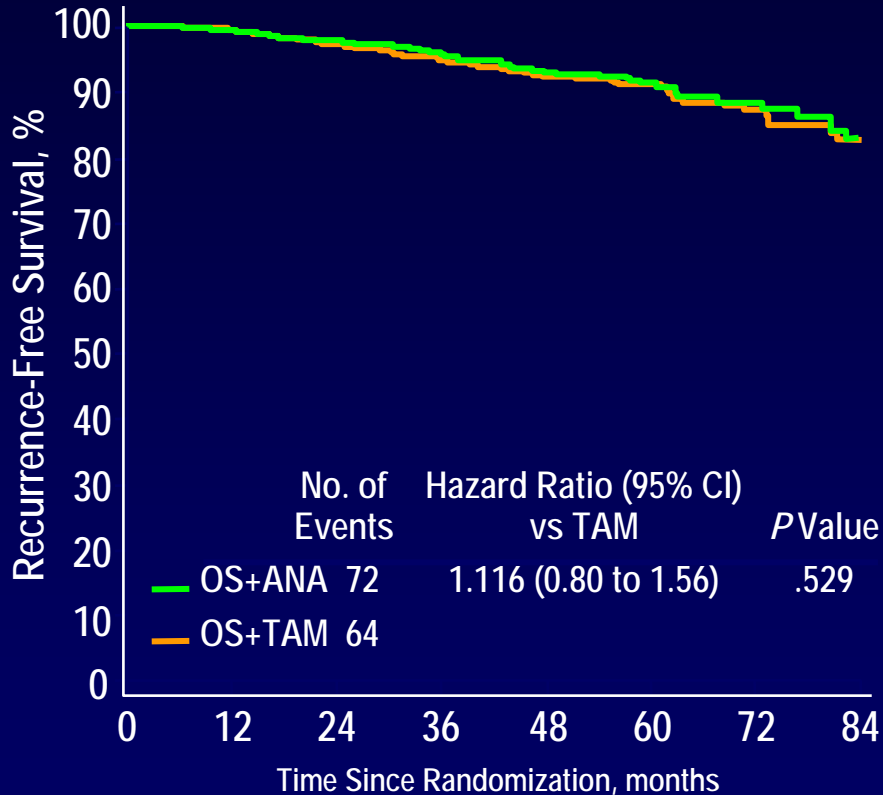
- **Initiate tamoxifen therapy**
- **Wait 1-2 years depending on risk, if menses not resumed**
- **Switch to AI**
- **Check gonadotropins and estradiol at 3 months, review and check that menses have not resumed**
- **Be aware of age related risk of return to fertility**

**Why Not Just Ablate/Suppress
Ovarian Function?**

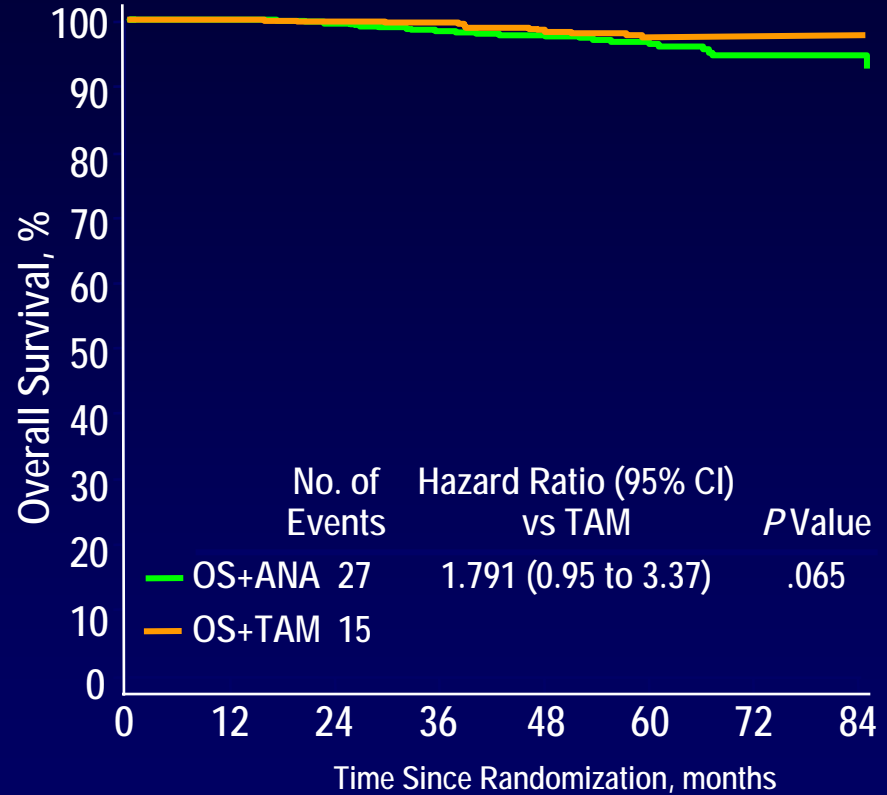
ABCSG 12 Outcomes

AIs No Different than Tamoxifen

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

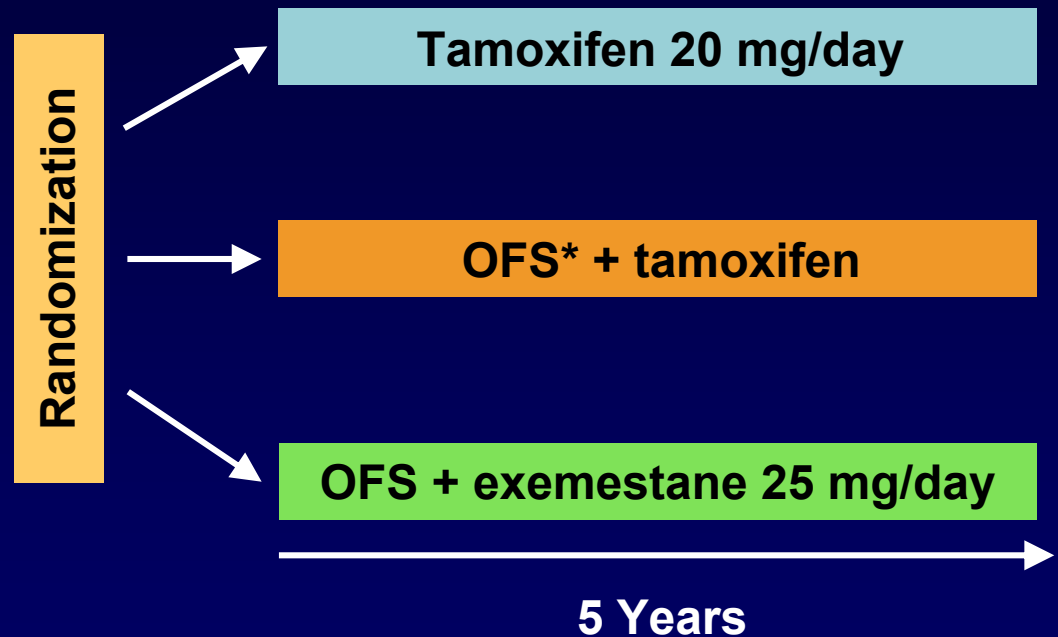
Enrolled as of 06/09: 2387

Eligibility:

Premenopausal

Estradiol (E₂) 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

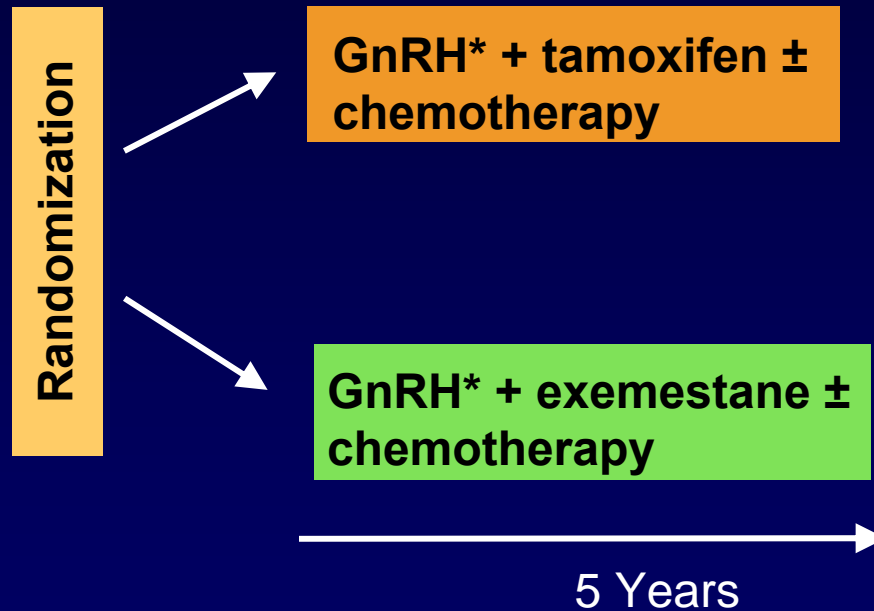
Enrolled as of 06/09: 2061

Eligibility:

Premenopausal

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

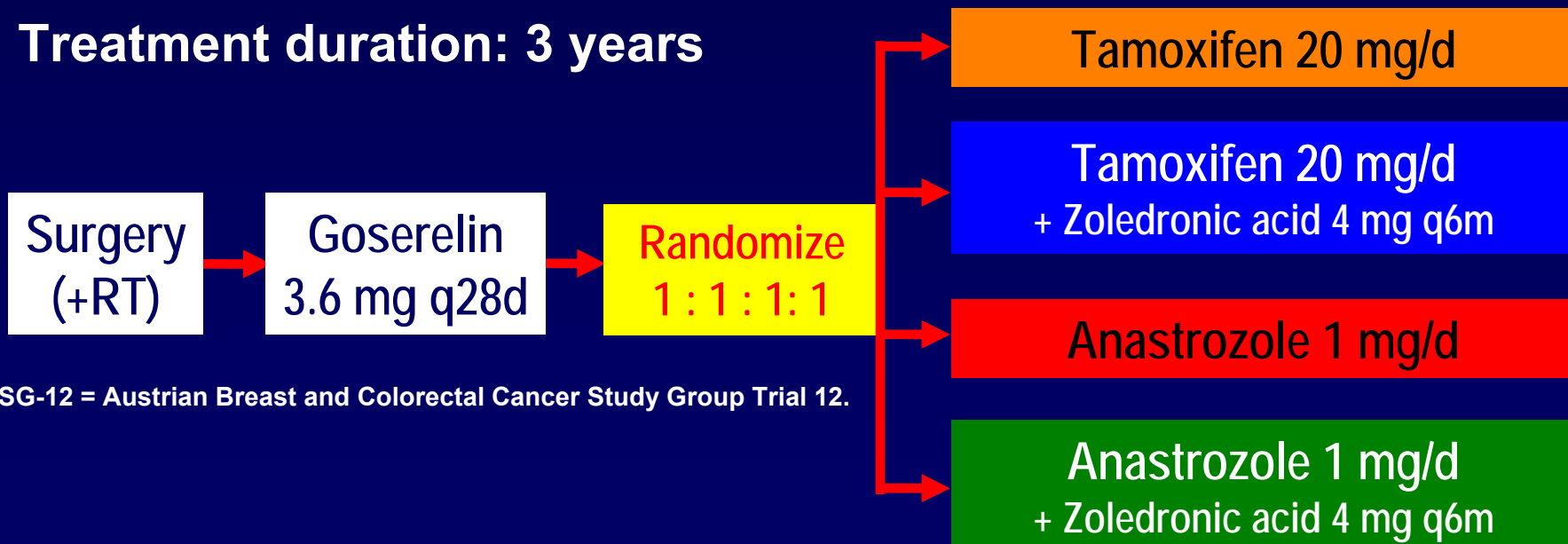
Candidates to begin GnRH analogue from the start of adjuvant therapy



*GnRH = triptorelin 3.75 mg by injection every 28 days for 5 years, but oophorectomy or radiation is allowed after 6 months.

ABCESG-12 Trial Design

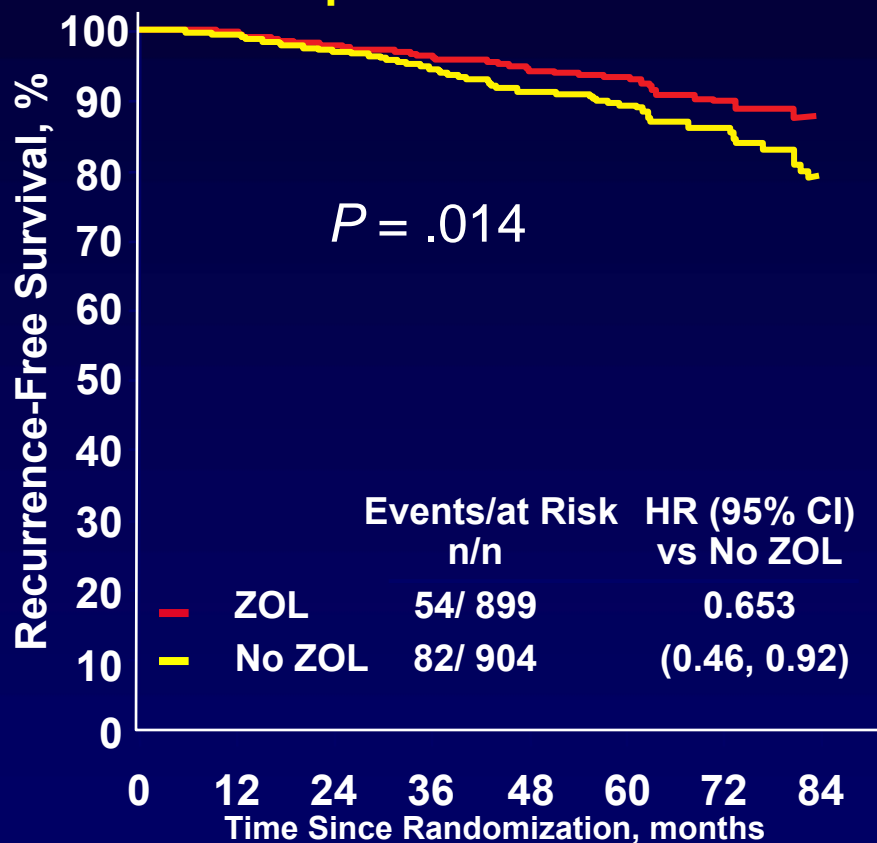
- Accrual 1999-2006
- 1803 premenopausal patients with breast cancer
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



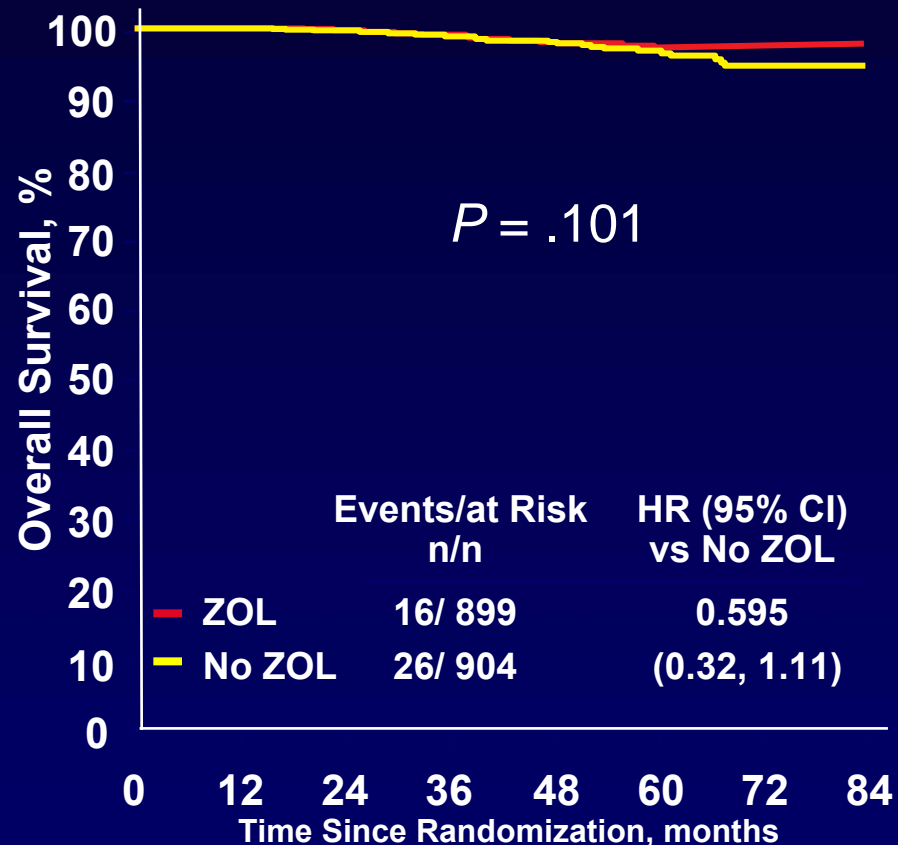
ABCESG-12 = Austrian Breast and Colorectal Cancer Study Group Trial 12.

Effects of Zoledronic Acid on Disease Outcomes

Relapse-Free Survival



Overall Survival



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

My Opinion

- **Start tamoxifen now**
- **Low risk of relapse in first 2 years**
- **Switch to exemestane after 2 years**
- **Check FSH and LH at 3 months**
- **If clearly postmenopausal continue on exemestane for 3 years, document BMD, and monitor/treat if indicated**
- **Review the literature in 5 years before stopping**
- **Watch the literature regarding adjuvant bisphosphonates**