



Breast Cancer Therapeutics: Changing Concepts

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Topics of Discussion

- **What happened to chemoprevention**
- **Molecular subsetting of breast cancer**
- **Genomic signatures for decision-making**

Risk Factors

BREAST CANCER RISK

- Female gender
- Increasing age (lifetime risk 12.3%; 1 in 8)
- Family history:
 - 1st degree relatives (mother, sister, daughter) esp. premenopausal with bilateral breast cancer
 - 20-30% of breast cancer patients have 1 or more relatives
- LCIS, ALH, ADH, DCIS
- Personal history of breast cancer
- Hereditary breast cancer: 5-10% (20,000)
 - BR CA 1 (87% lifetime risk, 50% by age 50) and 2: 15% of HBC (3,000)
 - Ashkenazi Jewish population—0.1 to 2% prevalence

Major Factors Absolute & Relative Risk Per Year

• BRCA 1/2 > 30	2%	20 x
• DCIS	2%	20x
• Breast XRT<30	2%	20x
• LCIS	1%	10x
• AH + Family HX	1%	8-10x
• AH	0.5%	4-5x
• Prior Inv Cancer	0.75%	5-8x
• Age > 60 (vs 30)	0.33%	10x

Minor Risk Factors Increase Relative Risk by Less than 2 fold but Often in the News

- **Alcohol**
 - *Increase relative risk (RR) by 10%/drink/day*
- **Estrogen and Progestin Replacement therapy**
 - *Increase in RR by 5% per yr of current use*
- **Estrogen Alone Replacement Therapy**
 - *~25% decrease to 2% increase in RR/yr current use*
- **Postmenopausal Obesity**
 - *30% increase in RR BMI >30 vs BMI < 25 kg/m²*
- **Sedentary Lifestyle**
 - *25-30% increase in RR 0 vs 3-4 hr per week exercise*

Risk Models and Counseling

Gail Model (II) Considers

- Current age
- Age at menarche
- Age at first live birth
- Number of 1st degree relatives
- Number of biopsies
- Presence of Atypical Hyperplasia
- Race

Does not take into account several major factors as well as common minor factors such as weight, physical activity and alcohol- New model proposed

***Gail et al. JNCI 81:1879, 1989,
Costantino et al JNCI 91: 1541, 1999.
Petracci and Gail JNCI 103:1037 2011***

Risk Reduction: Standard Approaches

Prevention Interventions Usually Geared to Level of Risk

- Very High Risk-2-3%/year (*BRCA mutation*)
 - Prophylactic Surgery
- High Risk 1-2%/year (*LCIS, AH + FH*)
 - Drugs or Prevention Trials
- Moderate Risk $>.33 < 1\%/yr$ (*AH or FH alone*)
 - Healthy Behaviors
 - Possibly tamoxifen under age 50
 - Possibly raloxifene or an aromatase inhibitor postmenopausal women

Surgical Risk Reduction Strategies For Very High Risk Women (2%/Yr)

- Oophorectomy premenopausal women (↓ risk by 50-70% even when women are given add back HRT)
- Mastectomy (↓ risk by $\approx 90\%$)
- Cost effective and likely to provide survival advantage

Rebbeck *et al.* NEJM 346:1616, 2002; JCO 23:7804, 2005

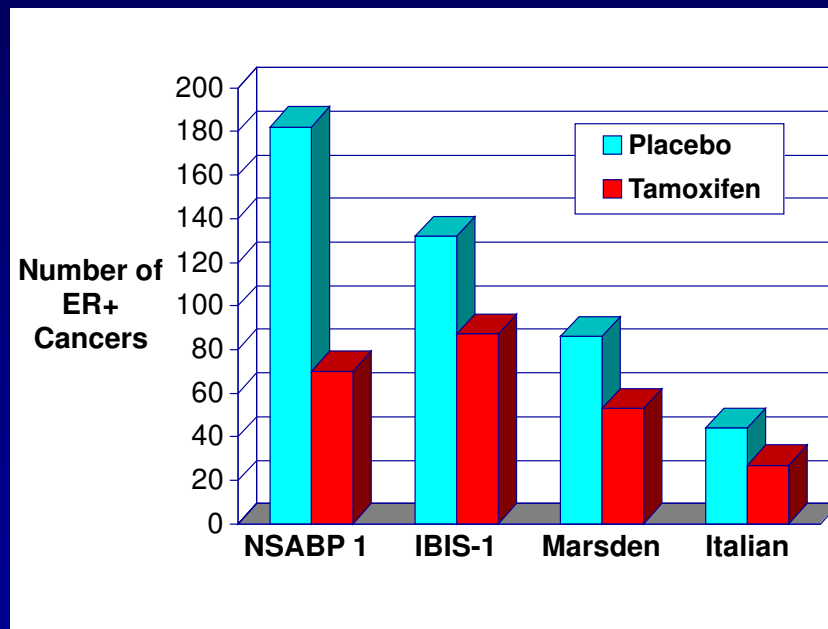
Hartmann *et al.* NEJM 340:77, 1999.

Warner *et al* J Clin Oncol. 2011;29:1664-9.

Grann *et al* Breast Cancer Res Treat 2011 125:837

Reduction of ER+ Cancers with Tamoxifen

Tamoxifen vs Placebo Pre & Postmenopausal



- 1/3-2/3 decrease ER+ cancers
- No decrease ER- cancers
- Menopause Symptoms
- Uterine effects/cancer
- Thromboembolism
- Cataracts
- No demonstrated survival advantage to date

Fisher et al. J Natl Cancer Inst
90:1371,1998.

Cuzick et al. Lancet 361:296, 2003

NSABP Protocol P-2 Schema

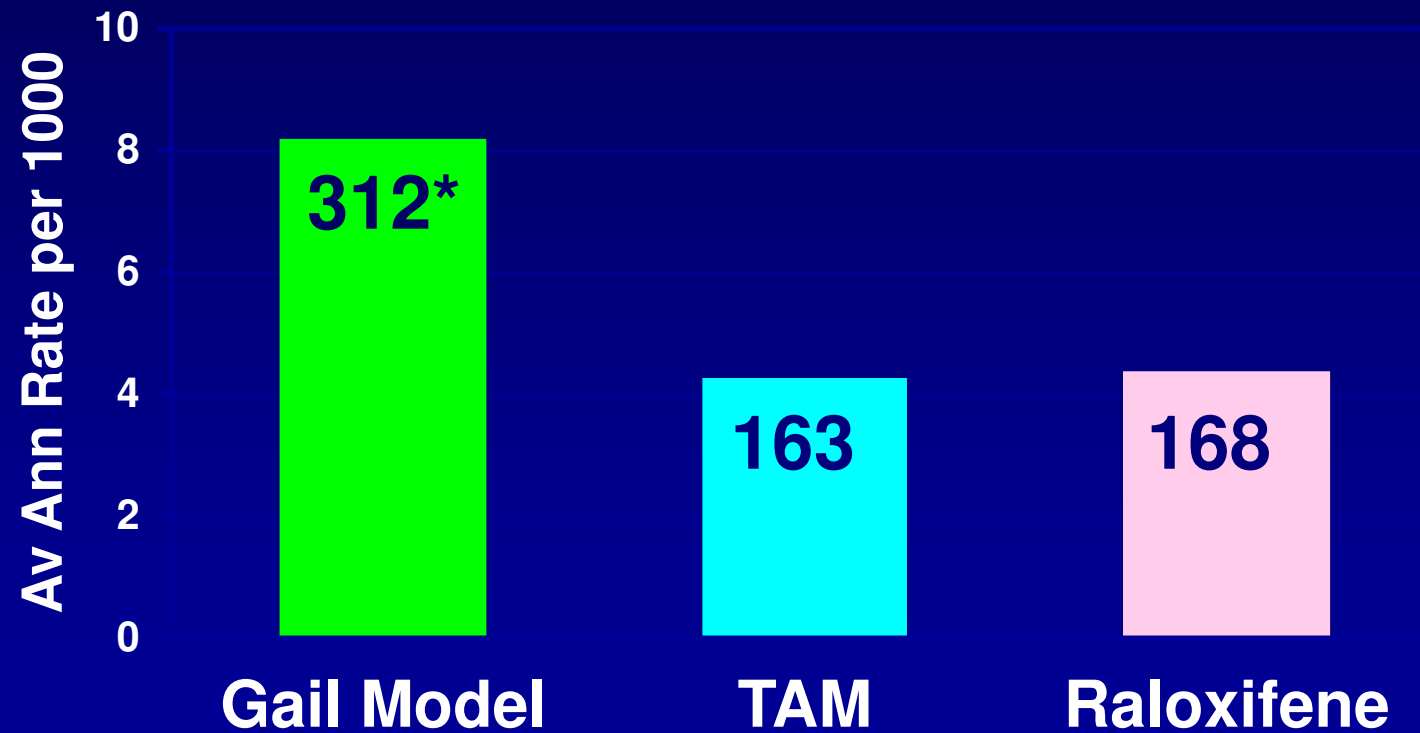
**Risk Eligible
Postmenopausal Women**

Stratification
Age
Gail model risk
Race
History of LCIS

Tamoxifen
20 mg/day x 5 years

Raloxifene
60 mg/day x 5 years

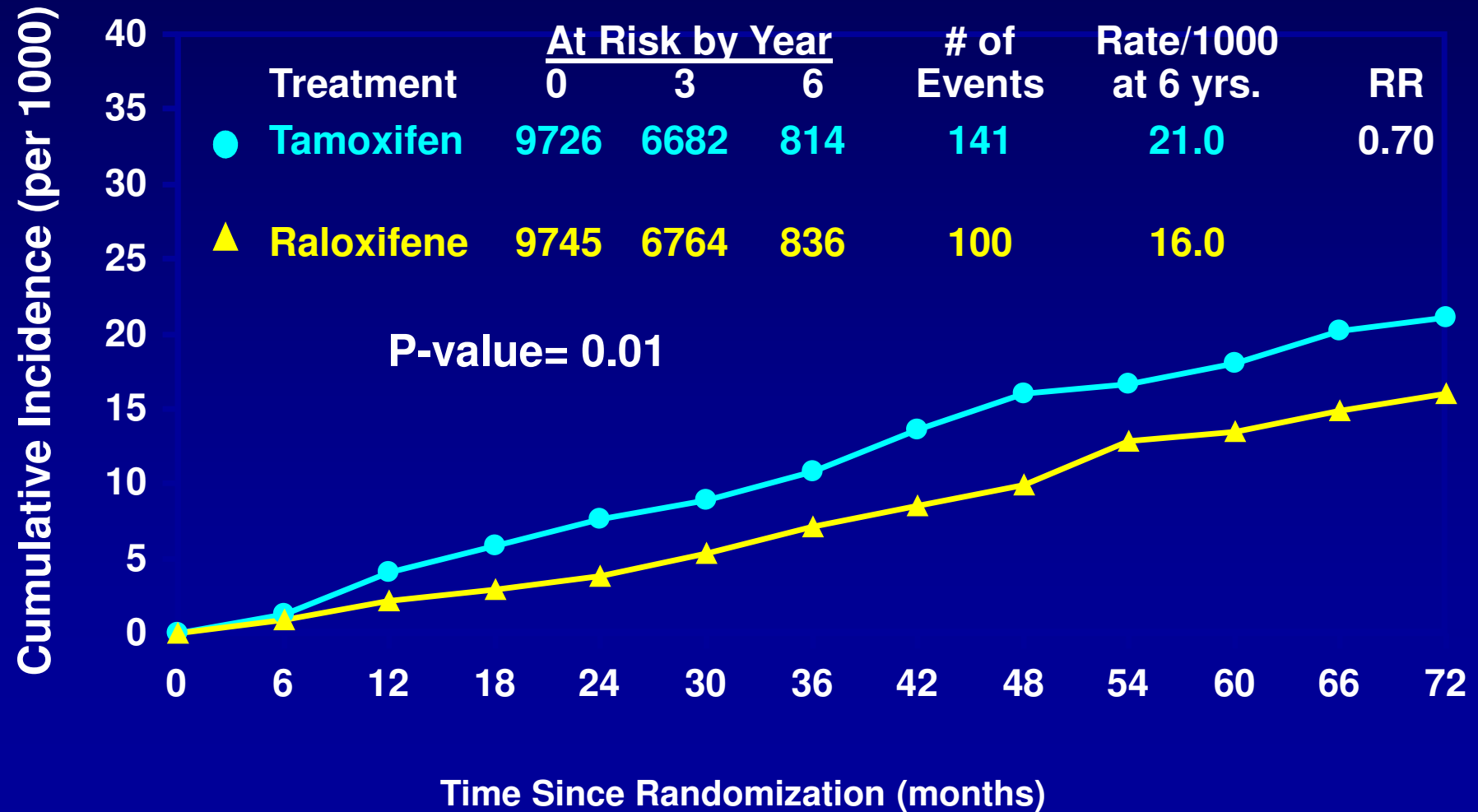
P-2 STAR
Average Annual Rate and
Number of Invasive Breast Cancers



* # of events

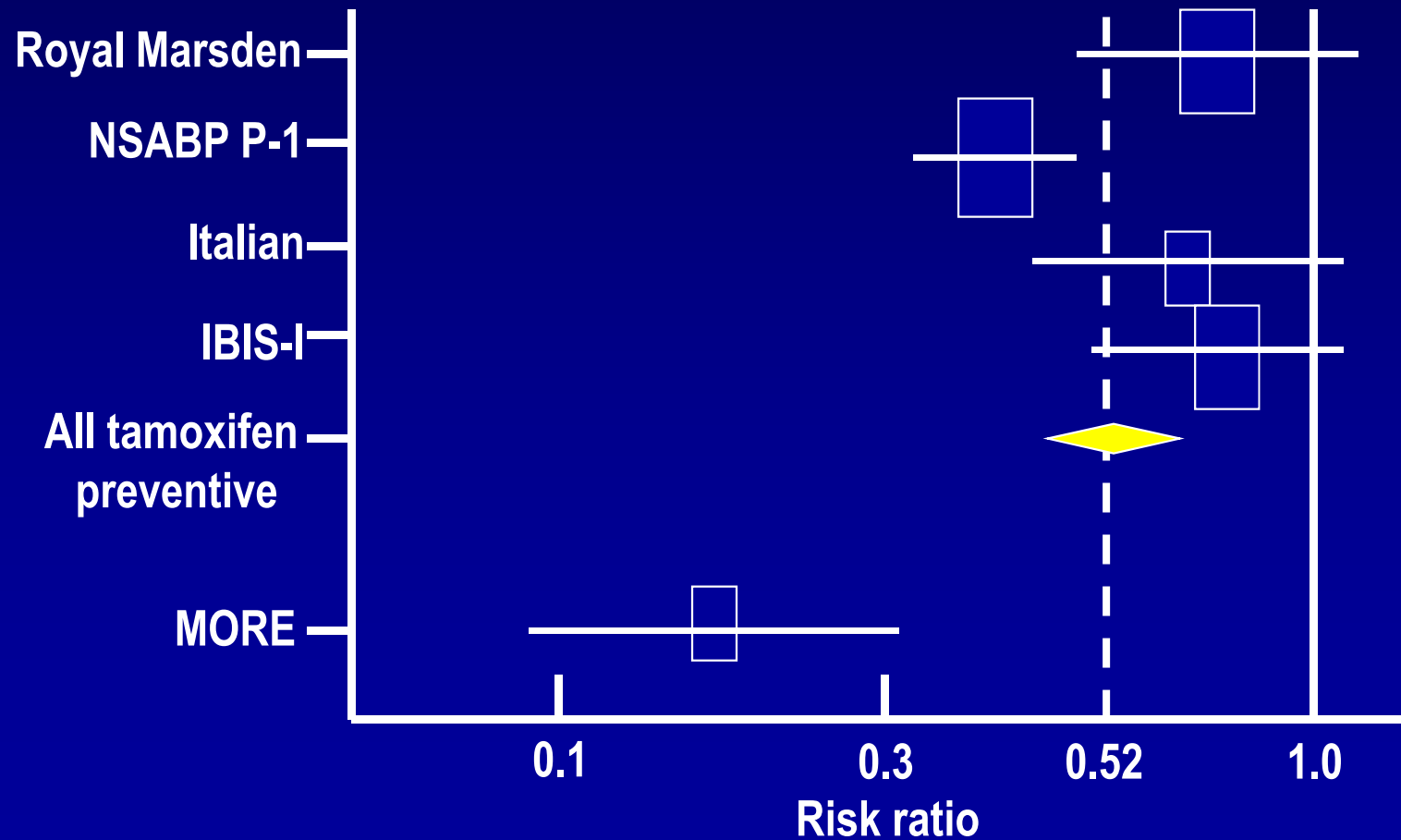
P-2 STAR

Cumulative Incidence of Thromboembolic Events



Meta-analysis of ER-positive breast cancer risk reduction trials using SERMs

Cuzick J et al. Lancet 361:296-300, 2003



Limitations of Using SERMs for Reduction of Breast Cancer Risk

- **Duration of benefit is uncertain**
- **Optimal duration of therapy is not known**
- **Optimal age to start therapy is unknown**
- **Acceptance may be poor among eligible subjects who will elect prophylactic surgery**
- **Toxicity is a concern in postmenopausal women (poor benefit:risk ratio)**

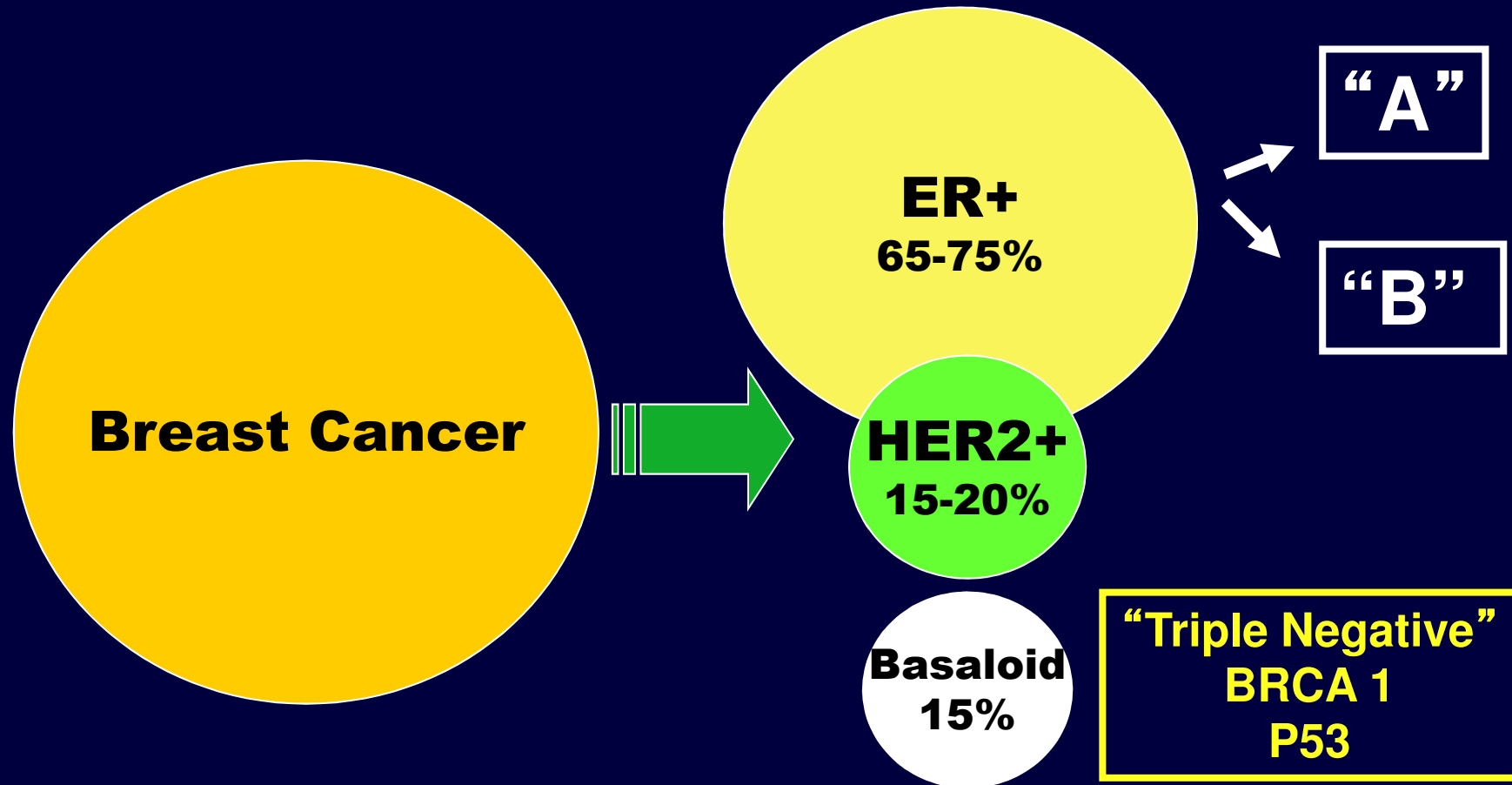
Barriers to use of tamoxifen

- Uptake of tamoxifen for breast cancer risk reduction has been poor (5 to 45 percent of eligible women)
- Most common reason for refusing use of tamoxifen is fear of serious side effects such as uterine malignancy and thrombosis
- Non-life threatening toxicities (e.g., weight gain and depression) that do not occur with greater frequency with tamoxifen are *widely misunderstood* and *inaccurately attributed* to the drug contribute **to its lack of use**

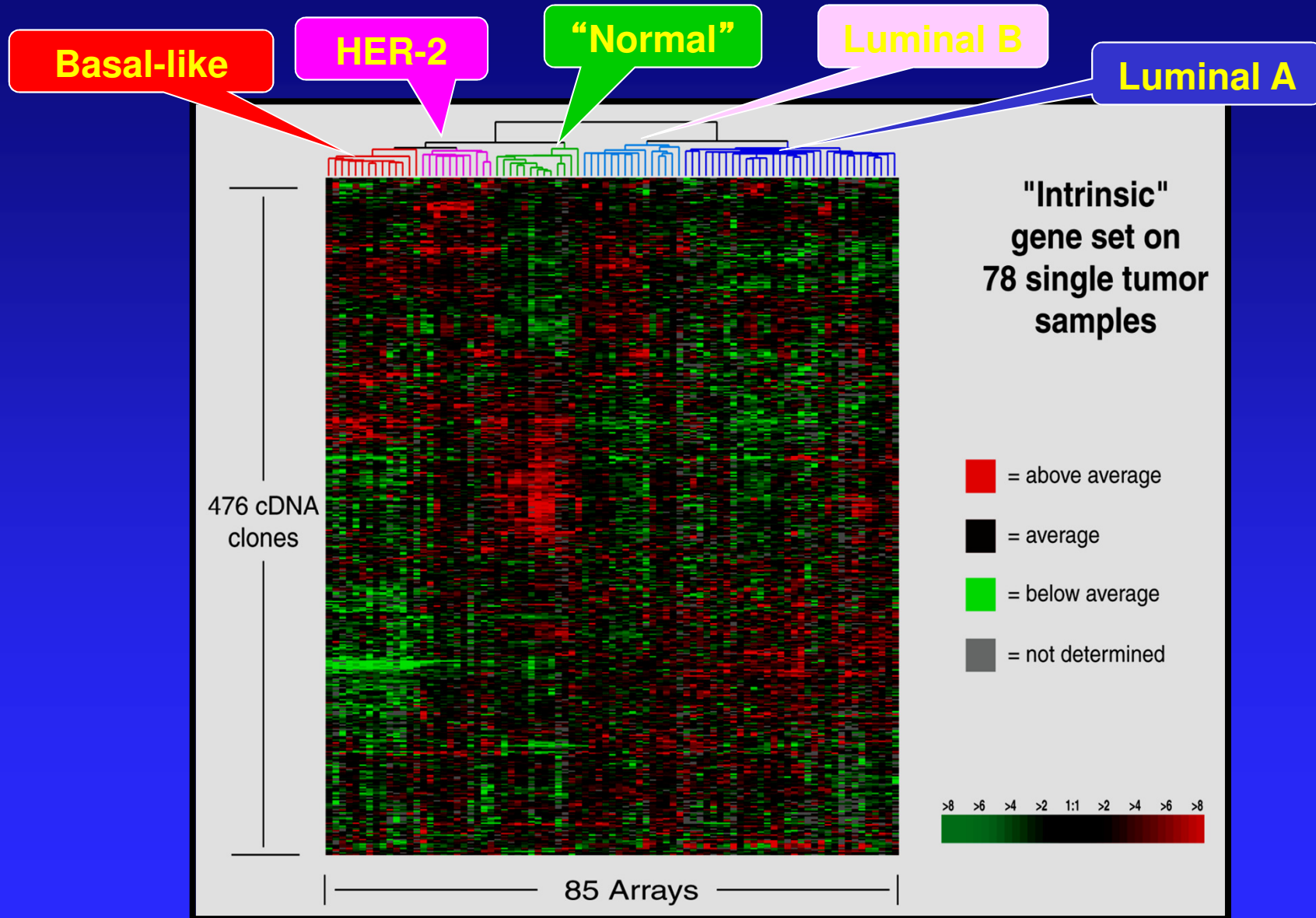
Possible benefits/barriers to the use of raloxifene for breast cancer risk reduction

- There may be differences between tamoxifen and raloxifene in the market's perception of their efficacy and safety
- More than 500,000 women take raloxifene for osteoporosis, and these prescriptions are provided mostly by gynecologists and primary care physicians
- Unknown whether MD's familiarity with raloxifene in the treatment and prevention of osteoporosis will lead to use for reduction of breast cancer risk

Most Important Paradigm Shift: Breast Cancer is not one disease

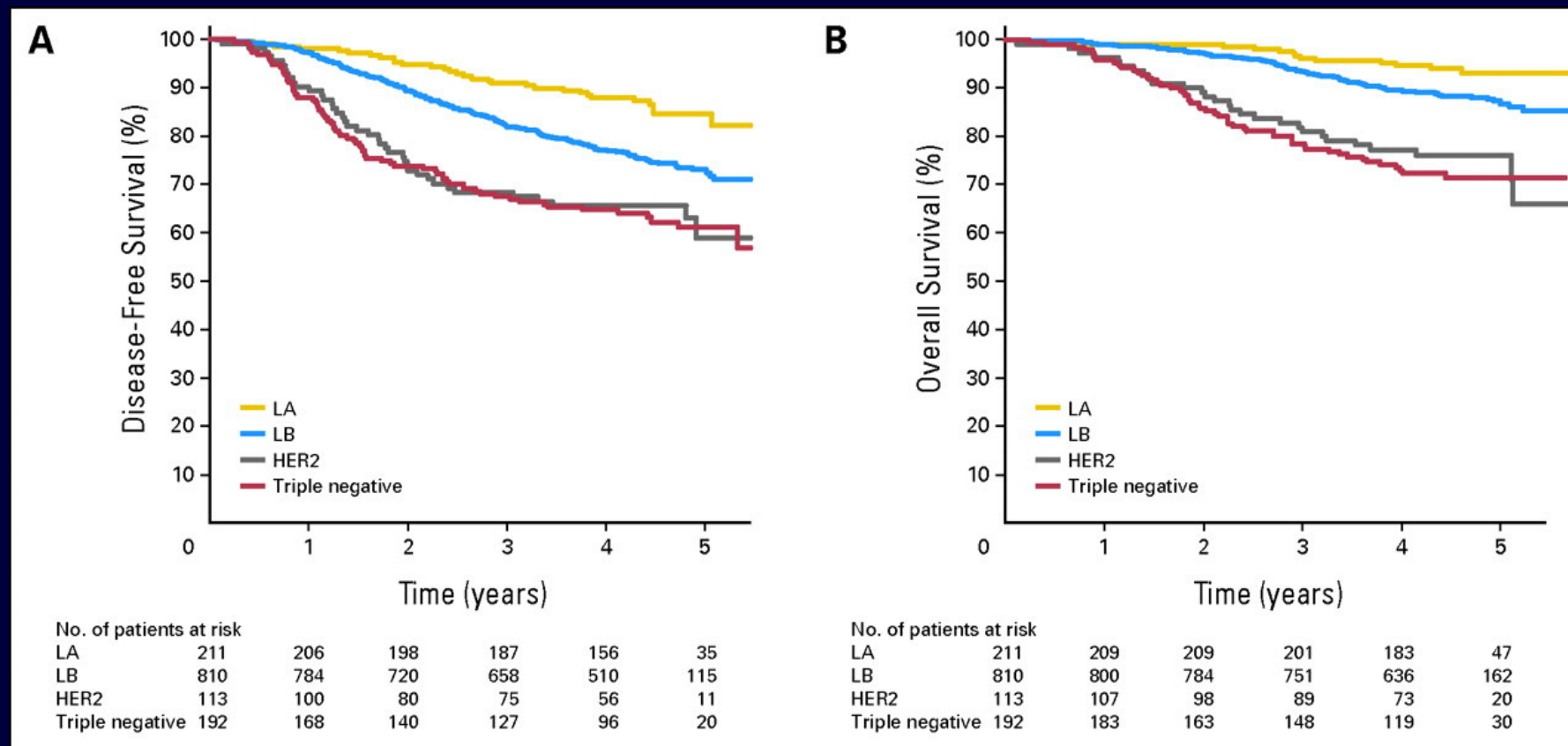


Molecular Portrait of Breast Cancers



Sorlie T et al, PNAS 2001

DFS among Subsets



Luminal A: ER+ and/or PR+ and HER2 neg and Ki 67 < 13% (low)

Luminal B: ER+ and/or PR+ and HER2 pos or Ki 67 > 13% (high)

Early stage disease

Case 1

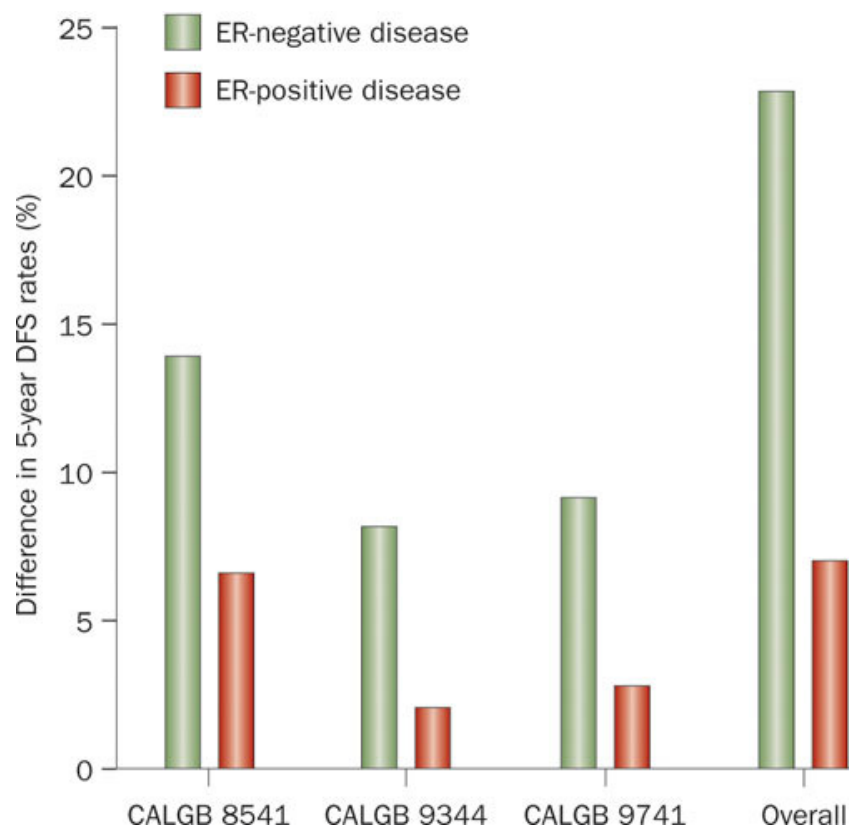
63 year old woman with invasive ductal carcinoma, minor co-morbid illnesses

- 1.8 cm
- Grade 2
- ER-positive (95%) / PR-positive (50%)
- HER2-negative
- Lymph node negative

What do you estimate her risk of recurrence in 10-years with endocrine therapy alone?

- A. <10%
- B. 10-15%
- C. 16-20%
- D. >20%

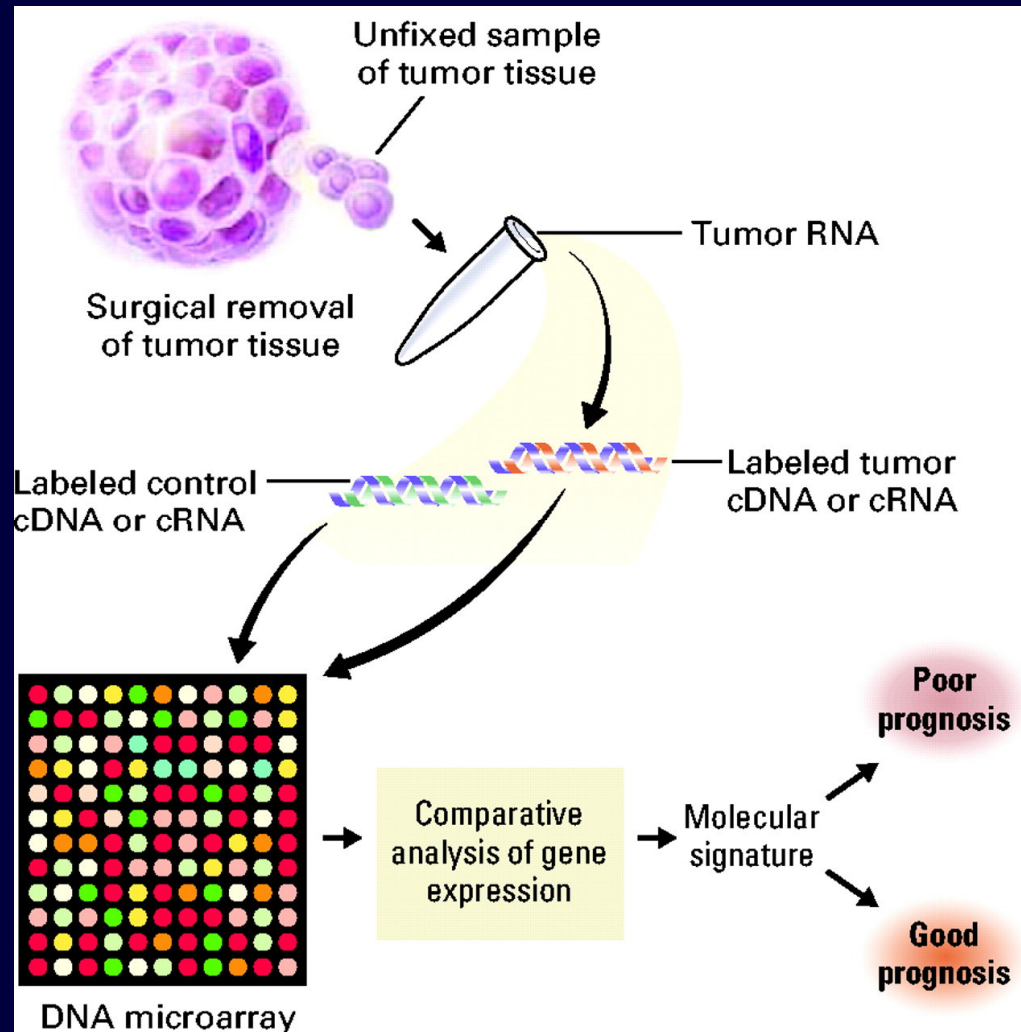
Figure 1 Difference in 5-year DFS rates between ER-positive and ER-negative patients receiving adjuvant chemotherapy in three CALGB trials.¹⁷



Bedard, P. L. & Cardoso, F. (2011) Can some patients avoid adjuvant chemotherapy for early-stage breast cancer?
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2011.19

**Adjuvant Online predicts her 10-year
risk of recurrence to be 12% with
endocrine therapy**

Gene Expression Profiles



van't Veer, L. J. et al. J Clin Oncol; 23:1631-1635 2005

21-Gene Recurrence Score

16 Cancer and 5 Reference Genes

PROLIFERATION

Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN

ER
PR
Bcl2
SCUBE2

HER2

GRB7
HER2

GSTM1

CD68

BAG1

INVASION

Stromolysin 3
Cathepsin L2

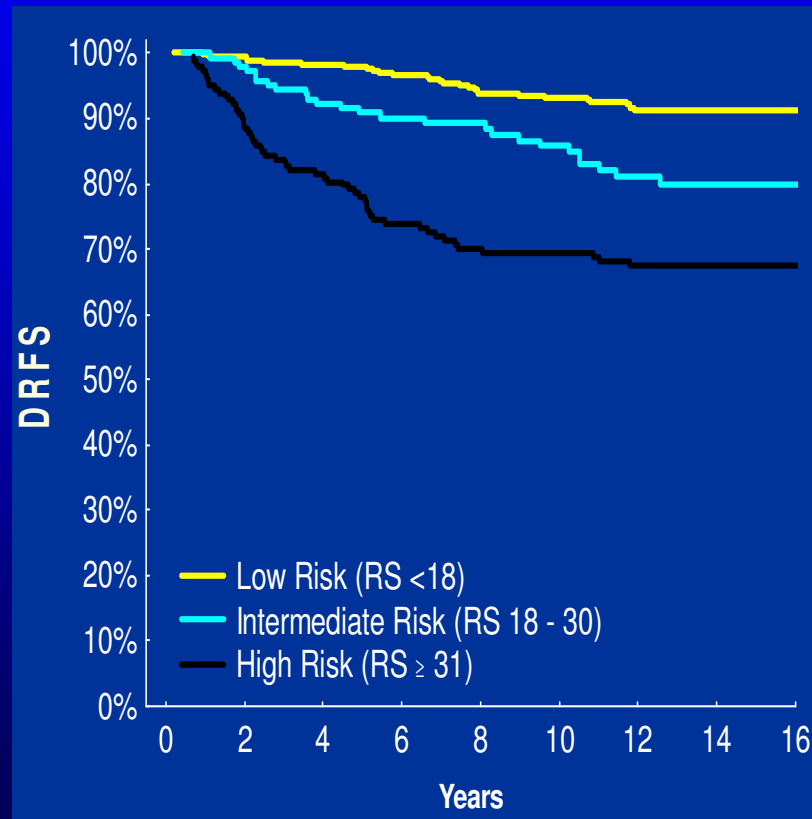
REFERENCE

Beta-actin
GAPDH
RPLPO
GUS
TFRC

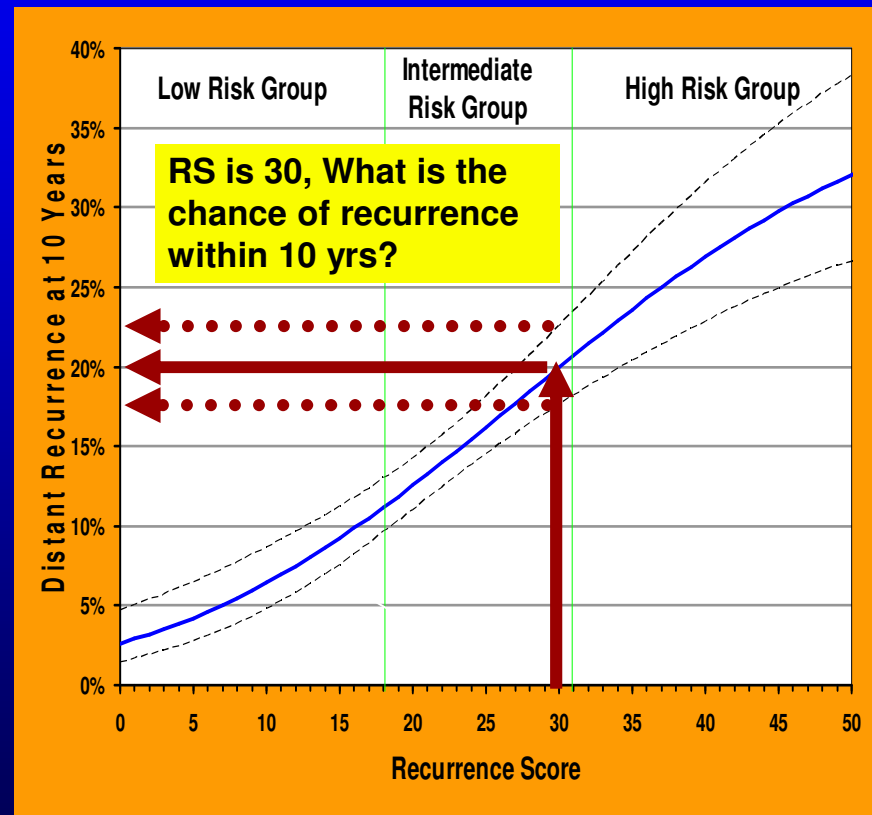
- **Best RT-PCR performance and most robust predictions**

NSABP B-14: Recurrence Score as a Prognostic Factor in Node (-), ER (+) Tamoxifen-Treated Patients

B-14 Validation Study



RS as a Continuous Variable

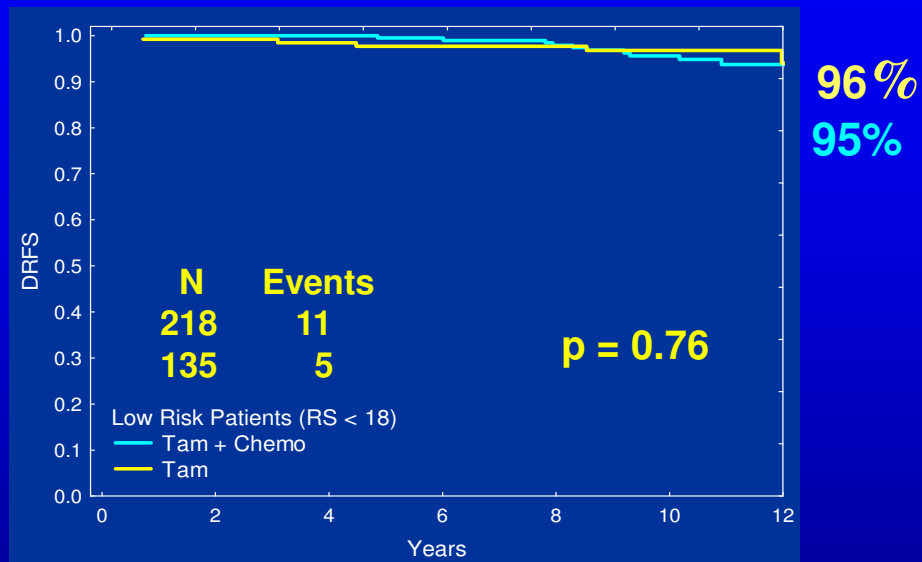


Her 21-gene recurrence score is 36

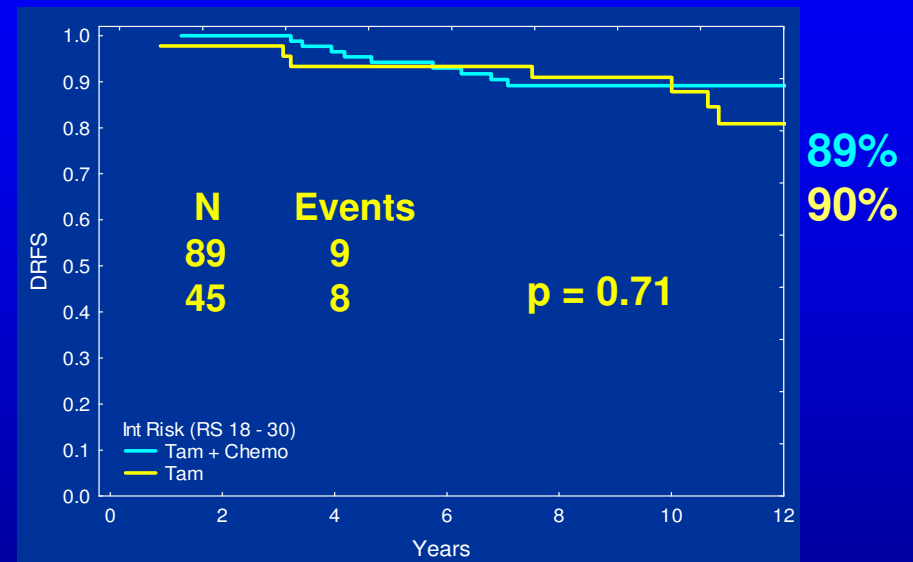
**Her 10-year risk of recurrence is 25%
with tamoxifen**

B-20 Chemotherapy Benefit By Recurrence Score Category

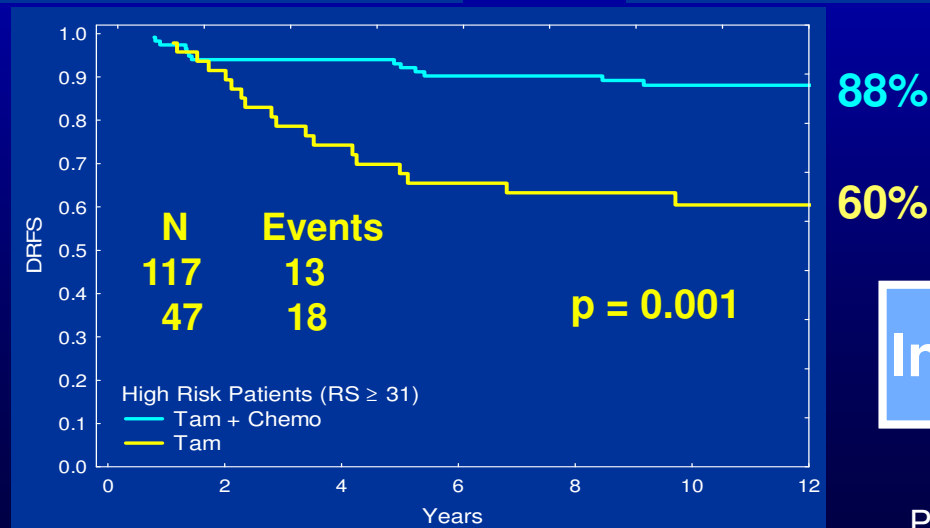
Low Risk (RS < 18)



Interm. Risk (RS 18–30)



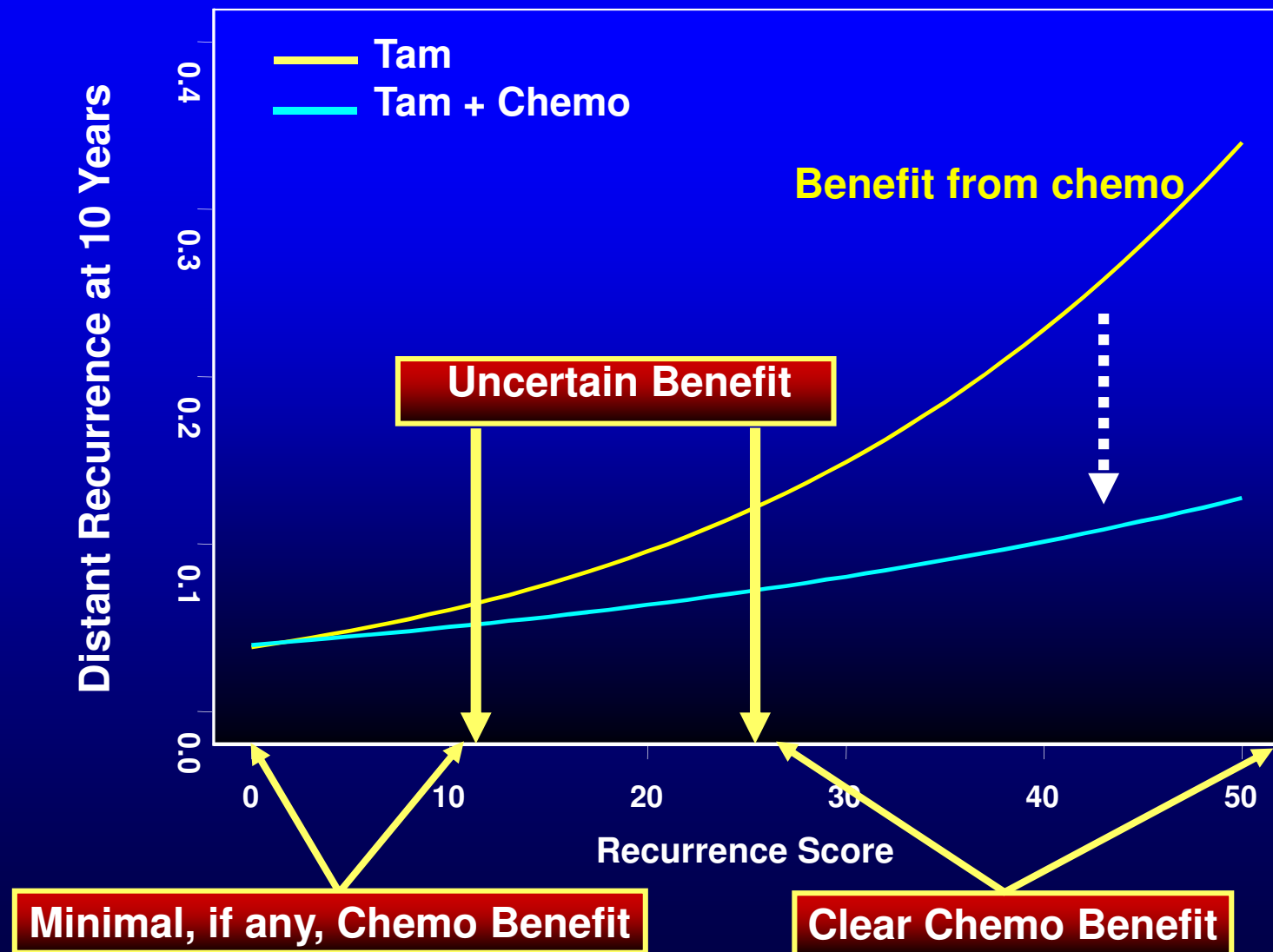
High Risk (RS ≥ 31)



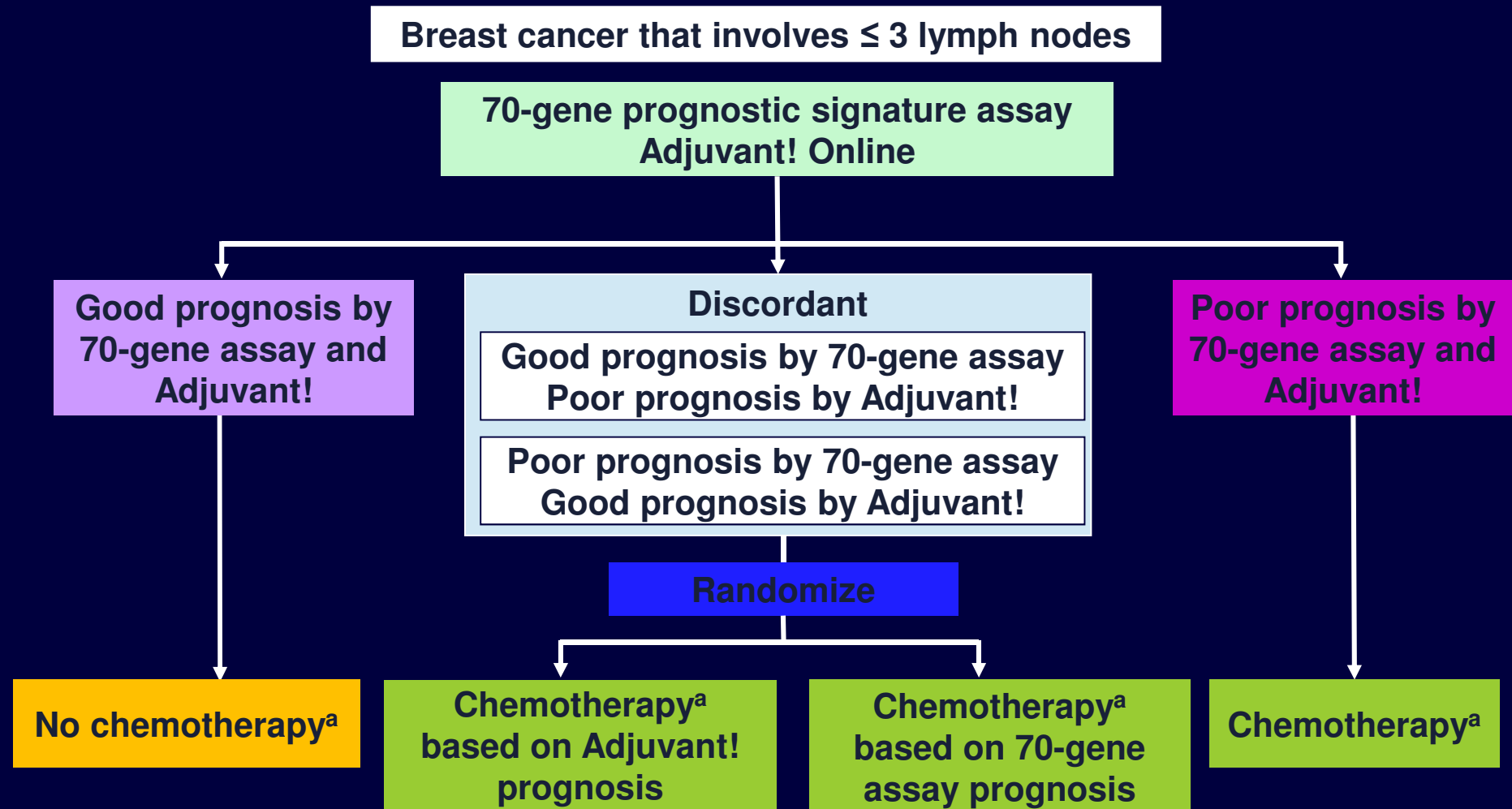
Interaction $p = 0.0368$

B-20 Results

Linear fit



Phase III MINDACT Trial: Trial Design



^a Patients with hormone receptor-positive disease also receive endocrine therapy.

Thank You

