The Challenge of Breast Cancer

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Harvard Medical School
Boston, USA -- October, 2011

The Scope of the Challenge

- In the United States alone, on an annual basis:
  - 180,000 cases of invasive disease
  - 60,000 cases of non-invasive disease
  - > 40,000 deaths
  - Cost to the health care system:
- Worldwide, on an annual basis:
  - > 1 million cases
  - > 400,000 deaths

What Is The Challenge?

Failure of early diagnosis to eliminate breast cancer deaths

Failure of initial systemic therapy

Limited use of therapy to prevent late recurrences

Failure to cure metastatic disease

BECAUSE OF…

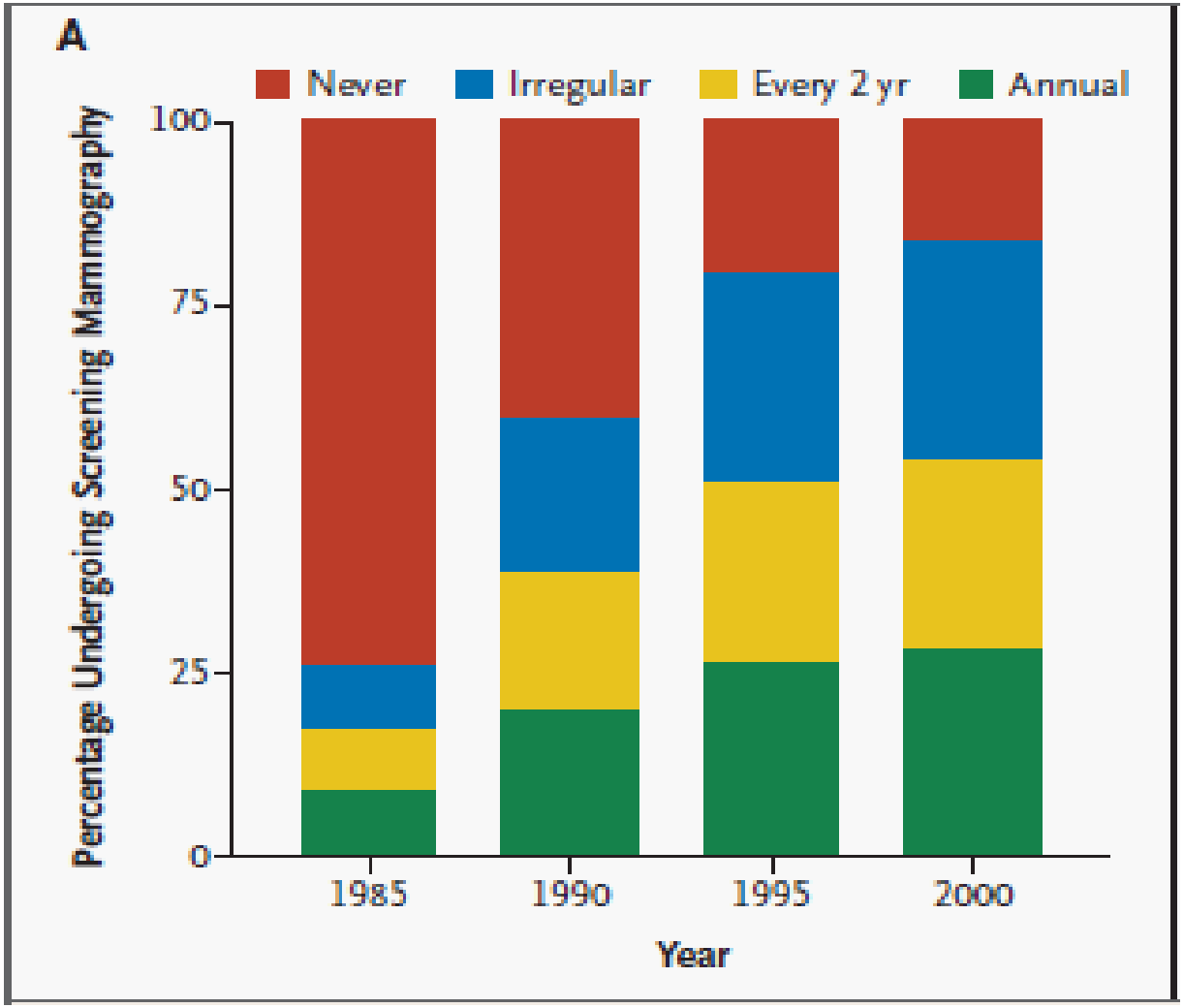
Tumor Heterogeneity

Drug Resistance

Early Metastatic Potential and Tumor Dormancy

Inadequate Access To Health Care

Changes In Use Of Mammography In The U.S. 1985-2000



From Berry et al
NEJM 2005

Average Annual Risk Reduction Of Regular Screening (age 40-59) Is Equivalent To:

- Putting on a helmet if you go for a 10 hour bicycle ride
- Canceling a 20-hr bicycle ride even if you are planning to wear a helmet
- Losing 1 oz of body weight and keeping it off

Estimates from Donald Berry, PhD
MD Anderson Cancer Center

If Mammography Can Detect 85% Of Breast Cancers, Why Isn't It Better?

- Failure to detect the most lethal cancers
  - The 15% not detected are distinct from the others
  - Triple negative cancers are more often mammographically occult and present as interval cancer
- Over-diagnosis of non-lethal cancers
  - Some would never be clinically relevant (because of regression, stability, or death from other causes)
  - Others would be equally curable if diagnosed at later point in time
- For some cancers, early is simply not "early enough"

We Need Better Screening Tools

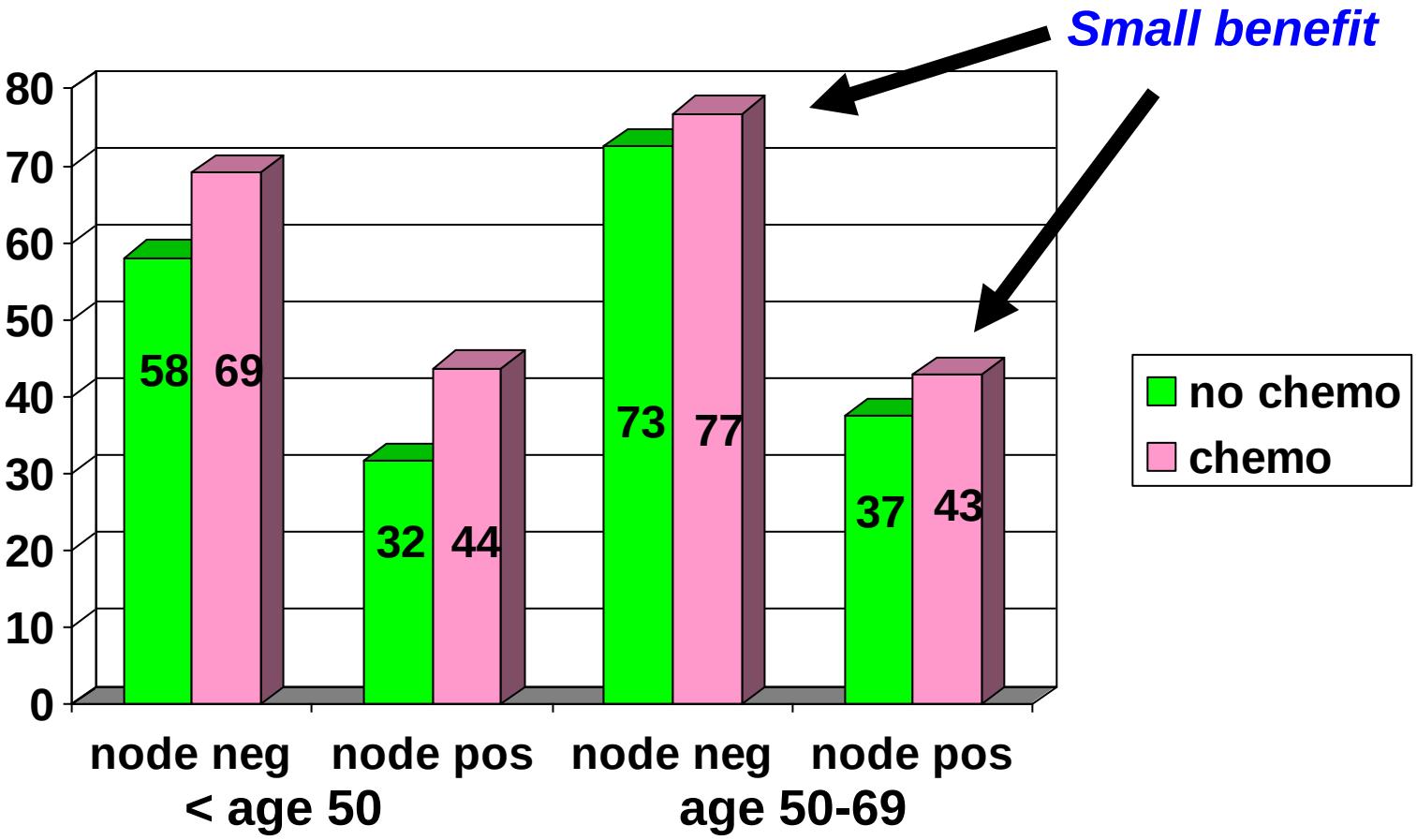
- Low cost
- High yield
- Capable of detecting the most lethal cancers
- Able to identify cancers earlier than mammography
- Well tolerated by patients

I have hope that such a tool can be developed, but we are asking for a great deal and it will not be simple

With Four Decades Clinical Trials Behind Us, Why Isn't Treatment Better?

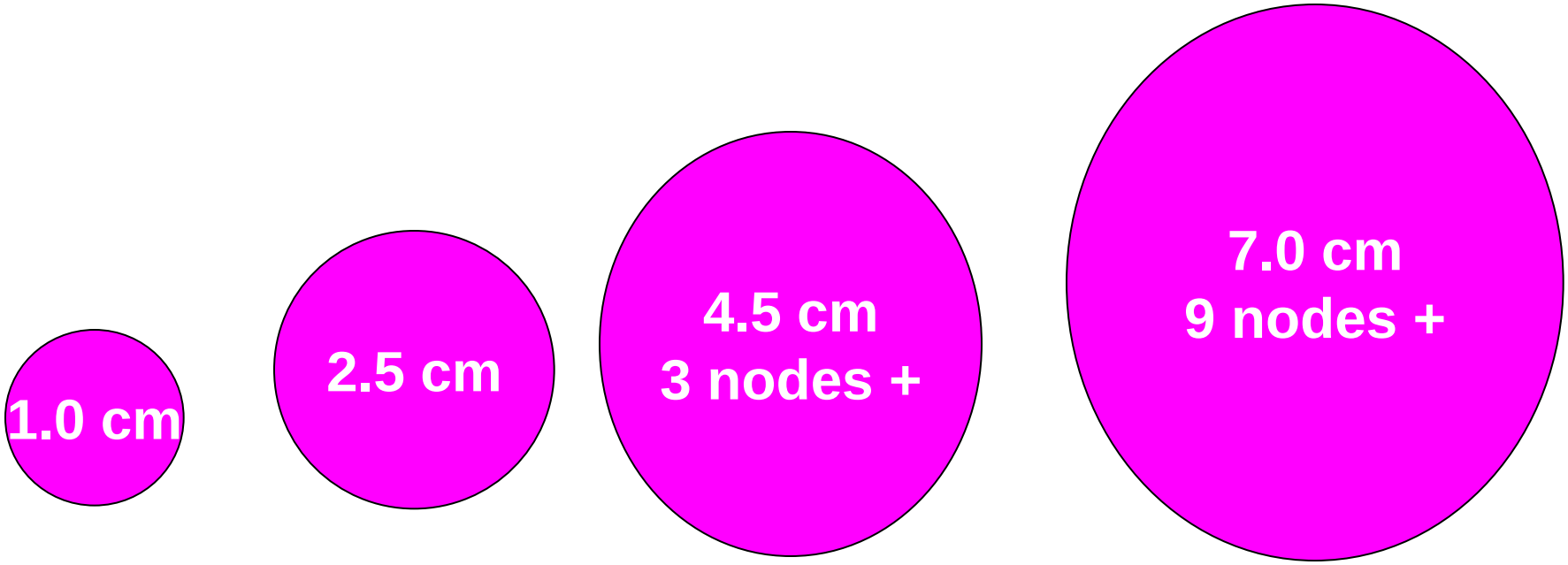
Polychemotherapy As Adjuvant Treatment: Oxford Overview

DISEASE FREE SURVIVAL AT 15 YEARS F/U



Smaller differences seen in overall survival

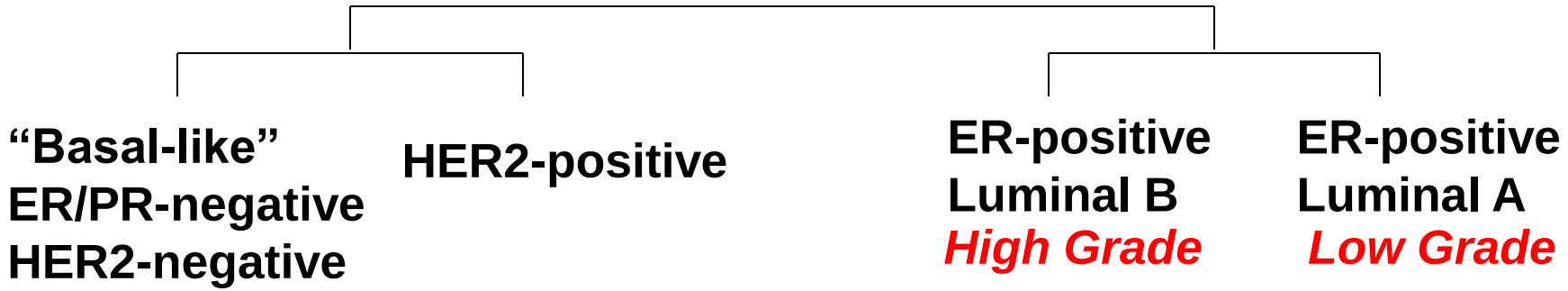
The Anatomic Approach: Almost All Decisions Based On Stage Of Disease

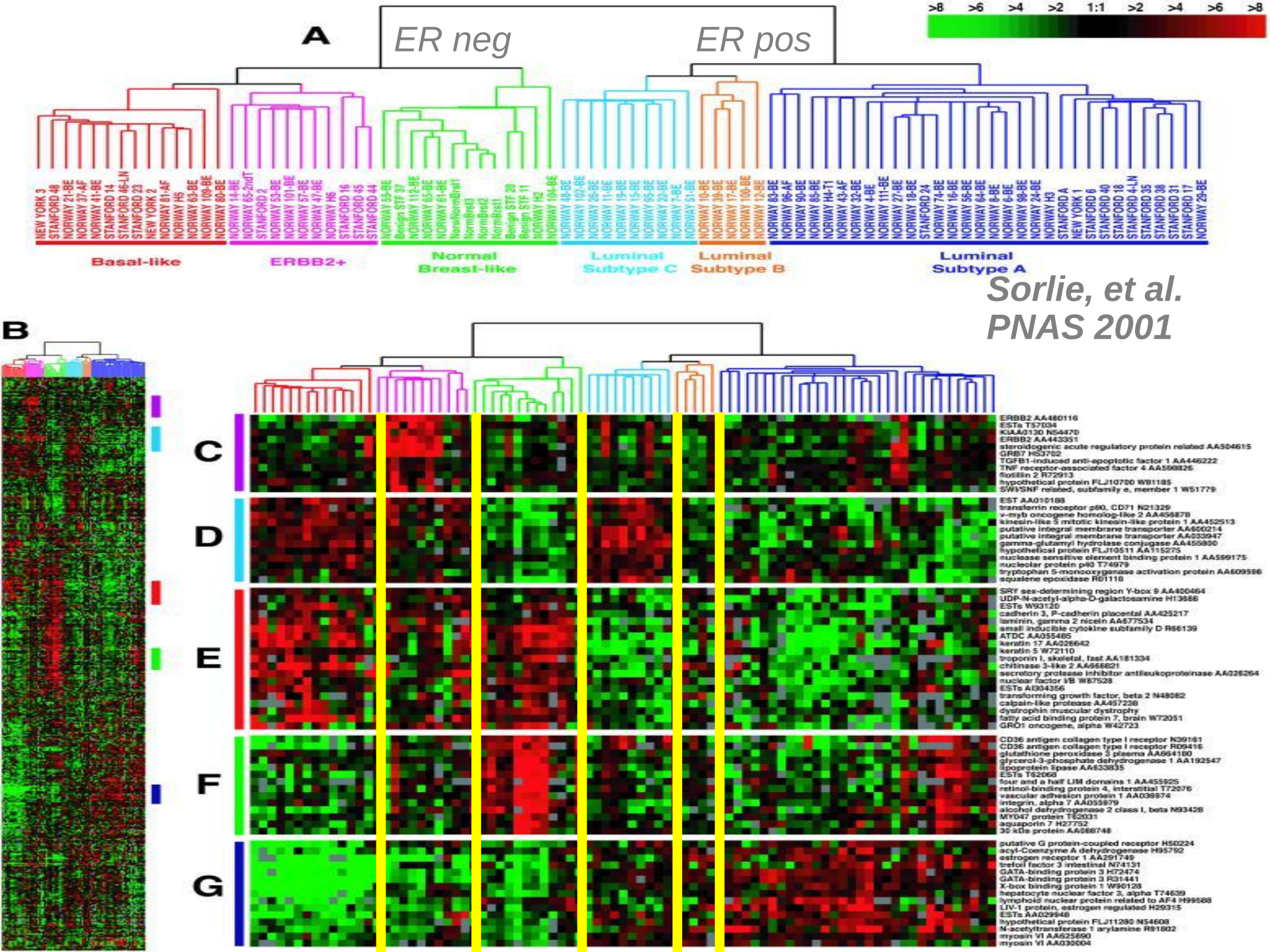


Treatment for Everyone!

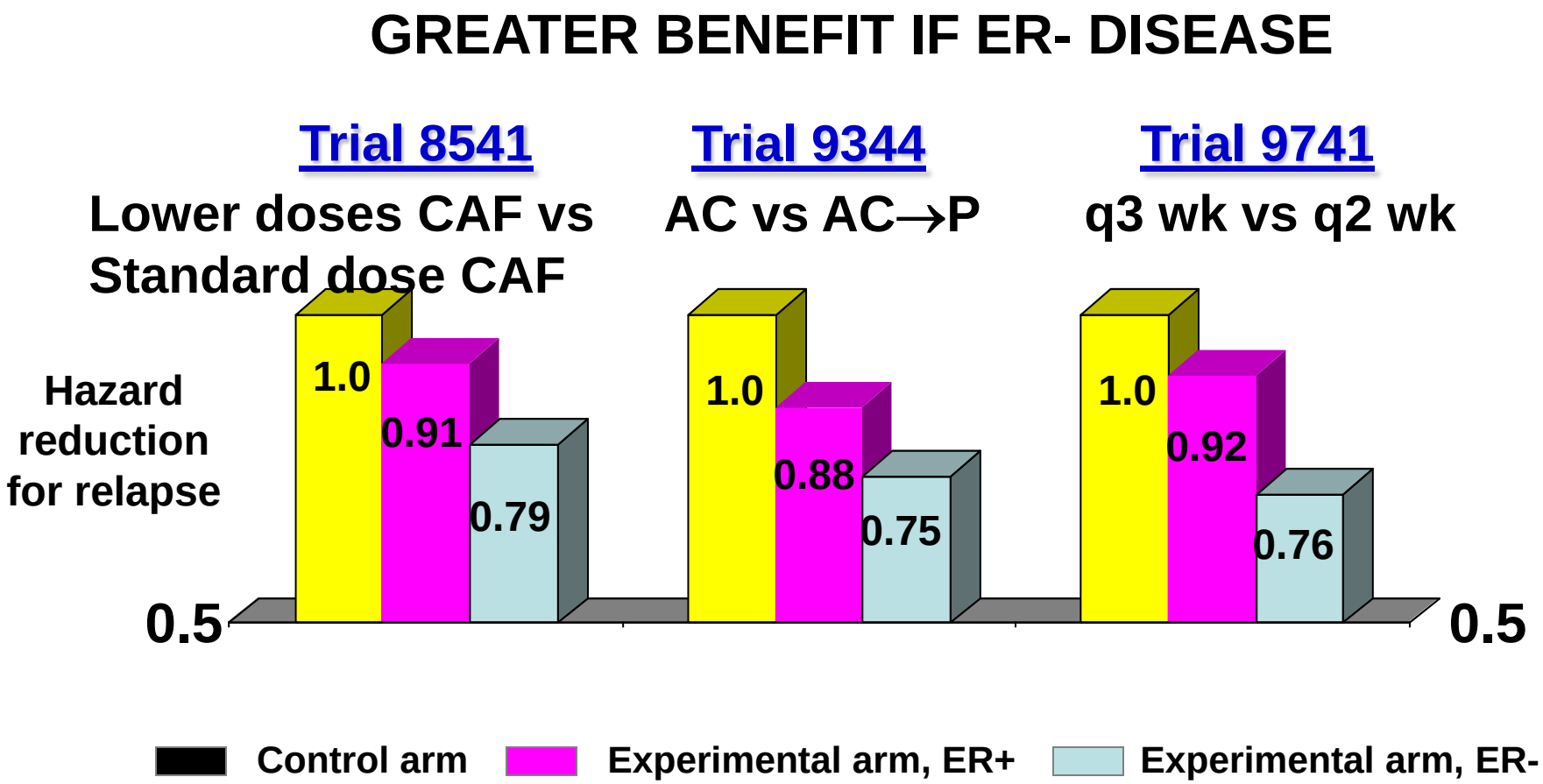
Breast Cancer is a Family of Diseases

- Convergence of clinical and genomic data
- Unclear how many distinct members of this family
- At a minimum:
  - HER-2 +
  - Basal-like or triple negative
  - ER + (luminal A)
  - ER + (luminal B)



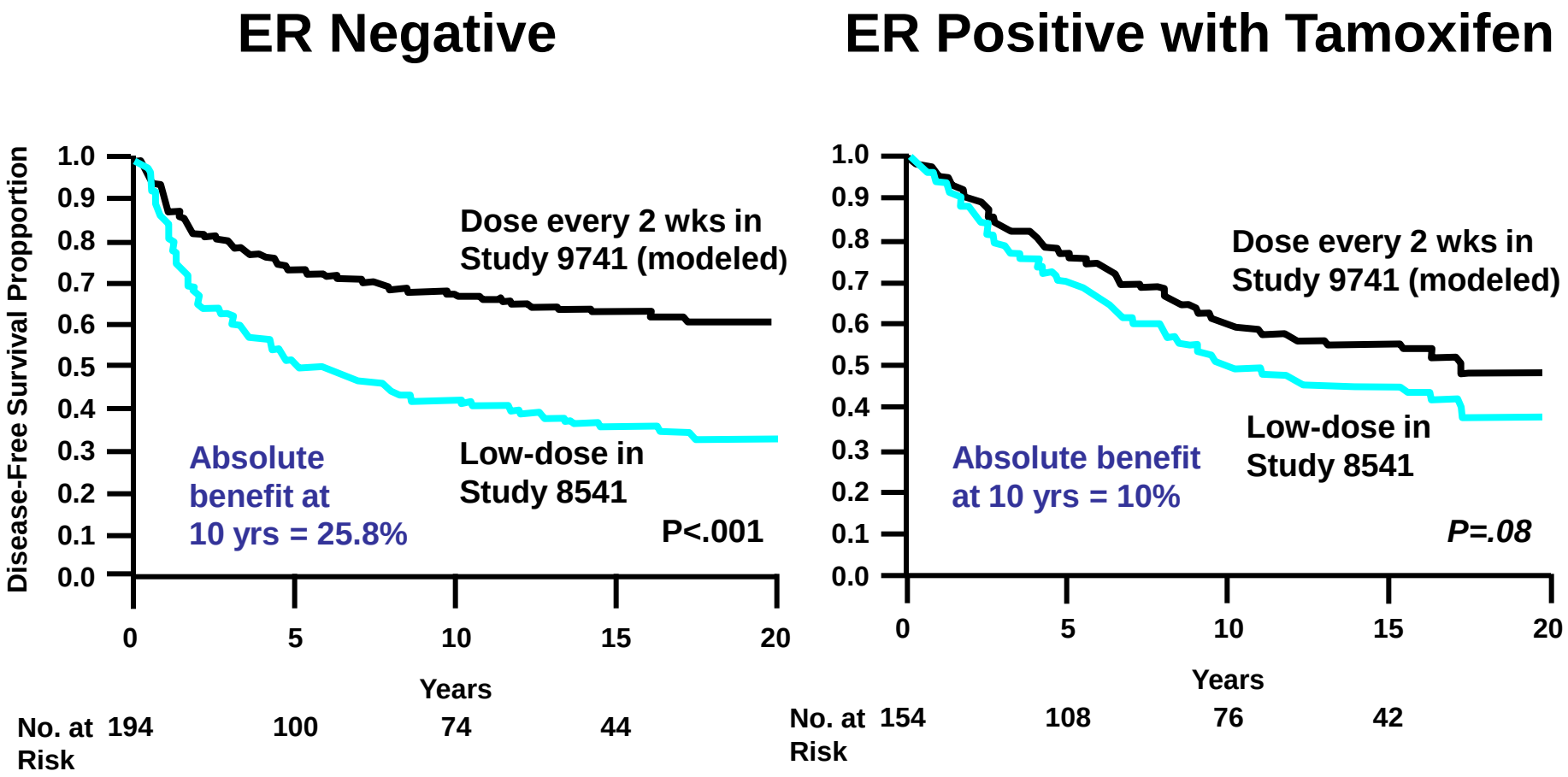

A
ER neg
ER pos
>8 >6 >4 >2 1:1 >2 >4 >6 >8
Basal-like
ERBB2+
Normal Breast-like
Luminal Subtype C
Luminal Subtype B
Luminal Subtype A
Sorlie, et al.
PNAS 2001
B
C
D
E
F
G

Degree of Improvement by Modern Adjuvant Chemotherapy Arm Differs by ER Status: Analysis of CALGB Database



Berry D, et al. JAMA 2006

Disease-Free Survival Low Dose CAF versus Same Patients on Dose Dense (Modeled)



Berry DA, et al. JAMA 2006

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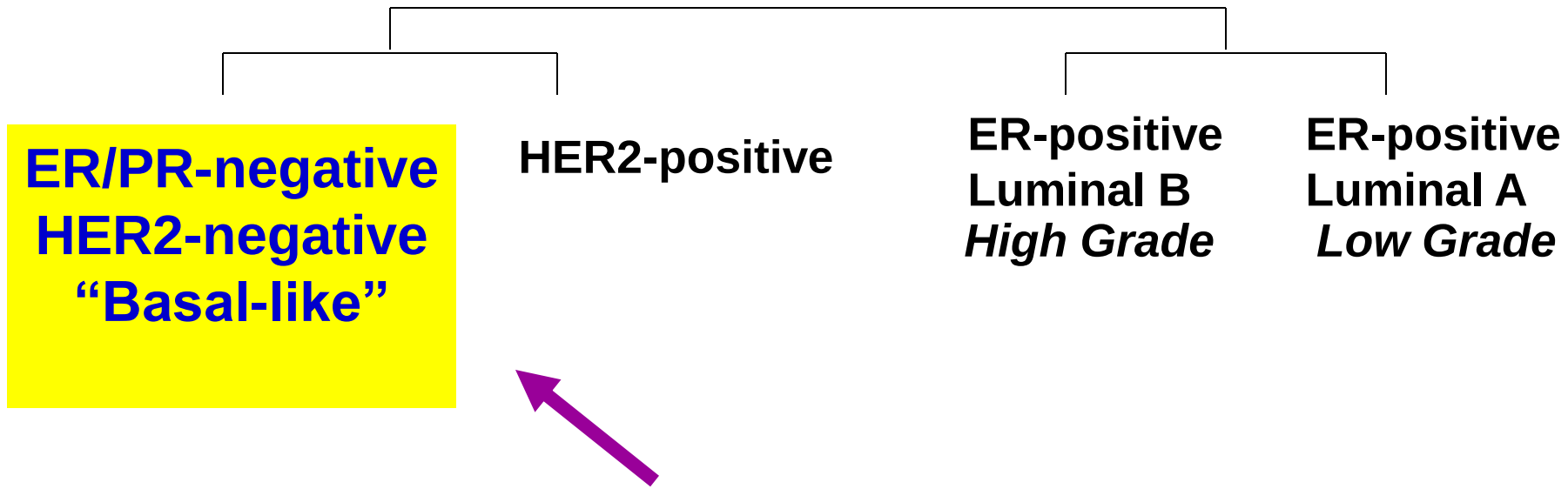
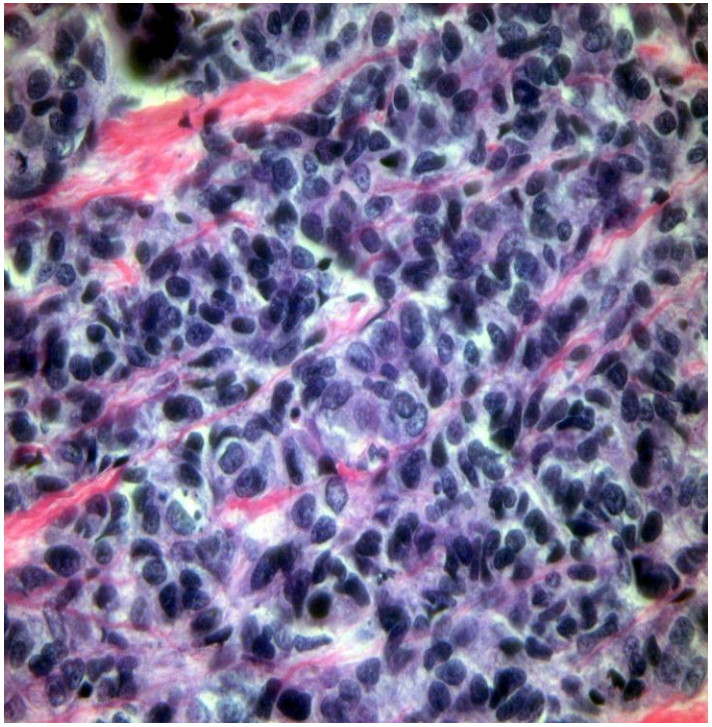


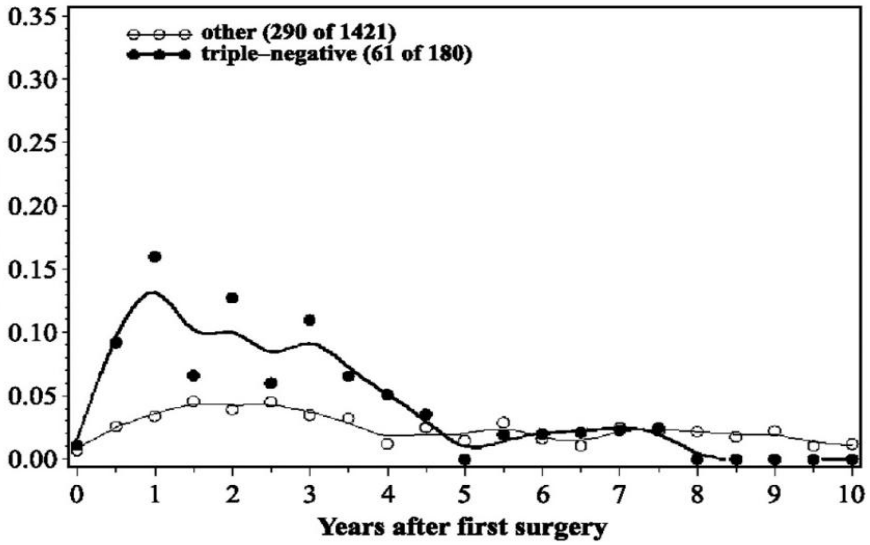
Triple Negative Breast Cancer

- 10-15% of all breast cancer
- 70-85% are basal-like on gene array degree of studies with some heterogeneity
- Majority BRCA-/- BC is TN
- High grade
- Scant DCIS component
- p53+
- Common immunohistochemical profile
- High degree of genomic instability
- Survival after recurrence



Triple Negative Breast Cancer: Distinct Behavior

Risk of relapse over time

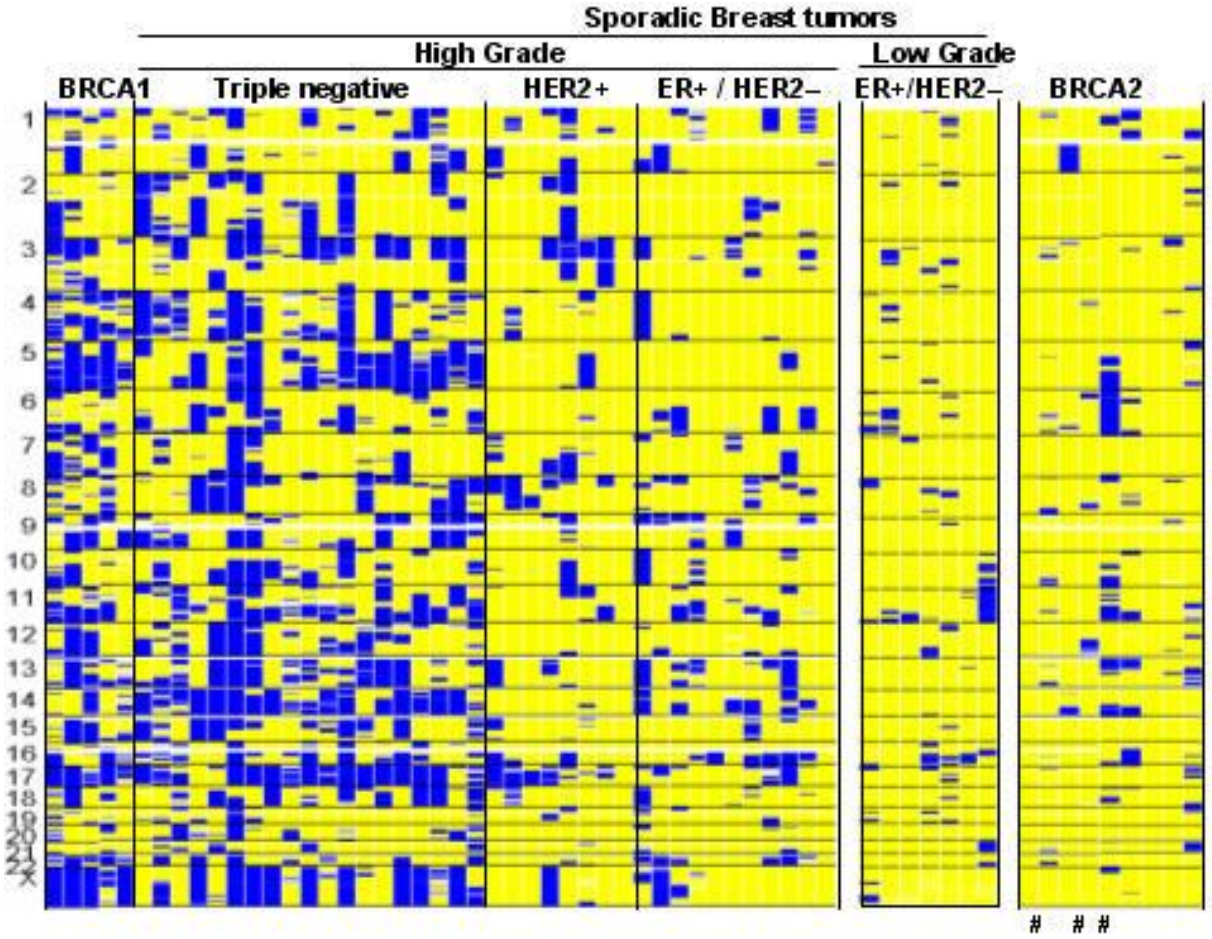


- **Relapse pattern:**
  - Higher risk, early timing
  - Sites of involvement differ from luminal:
  - CNS involved in up to 46%

Sites involved	N	Bone	Soft Tissue	Viscera
TNBC	79	13%	13%	74%
ER+	123	39%	7%	54%
HER2+	78	7%	12%	81%

Dent, Clin Cancer Res 2007; Liedtke, JCO 2008; Lin, Cancer 2008

Allelic Loss in Breast Cancer Subtypes and In BRCA1 and BRCA2 Mutation Carriers



No allelic loss (heterozygosity intact)

Allelic loss (LOH)

- BRCA1 and Triple Neg tumors show similar patterns
- BRCA2 tumors are not similar

Silver, Wang, Richardson, Iglehart Dana-Farber SPORE in Breast Cancer

Preoperative Cisplatin (CDDP) in Triple-Negative Breast Cancer

- N = 28
  - > 2-cm stage II/III triple negative
- Single-agent cisplatin 75 mg/m^2 q3w x 4 cycles prior to surgery

Response:

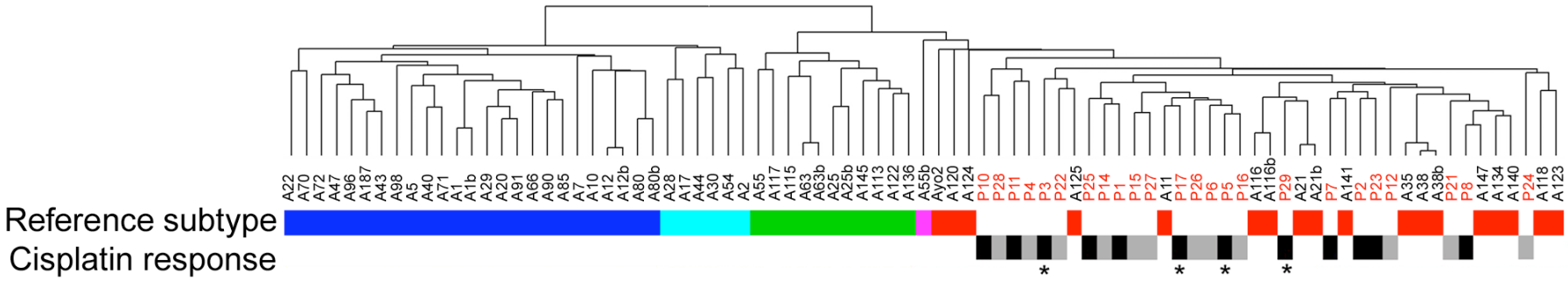
Pathologic CR	6 (22%)
Clinical CR	4 (14%)
Clinical PR	10 (36%)
Stable Disease	5 (17%)

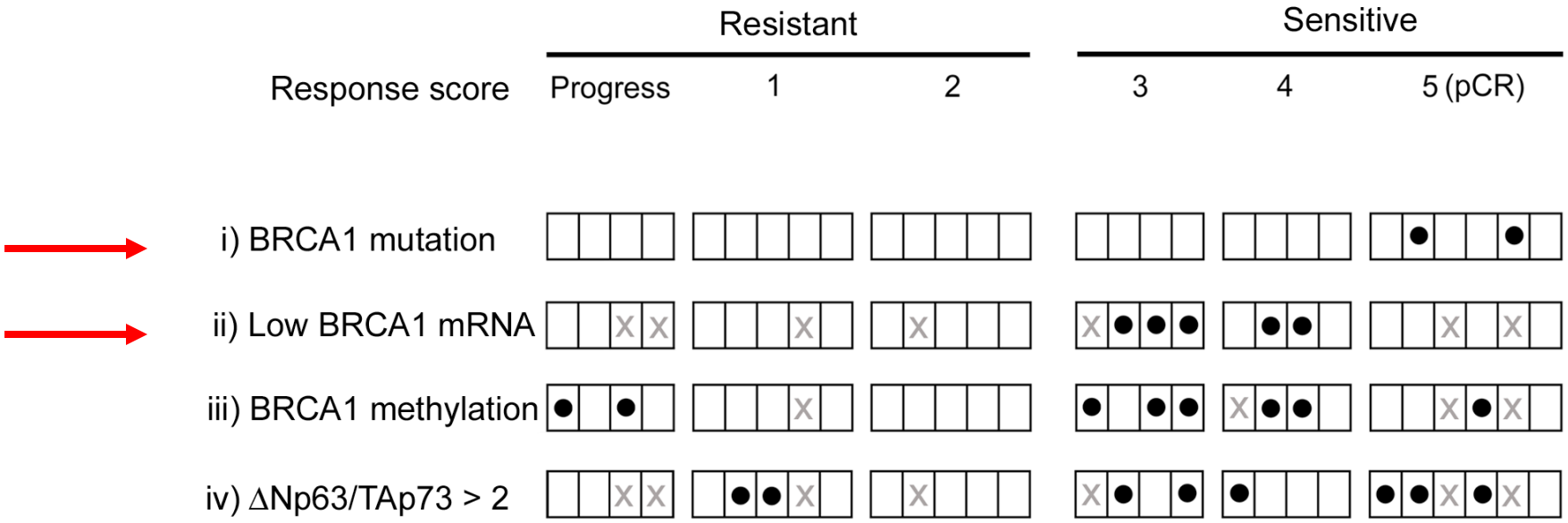
In a second trial using CDDP + bevacizumab, response was similar

- **Age associated with pCR (P < .04)**

Silver et al, JCO 2010

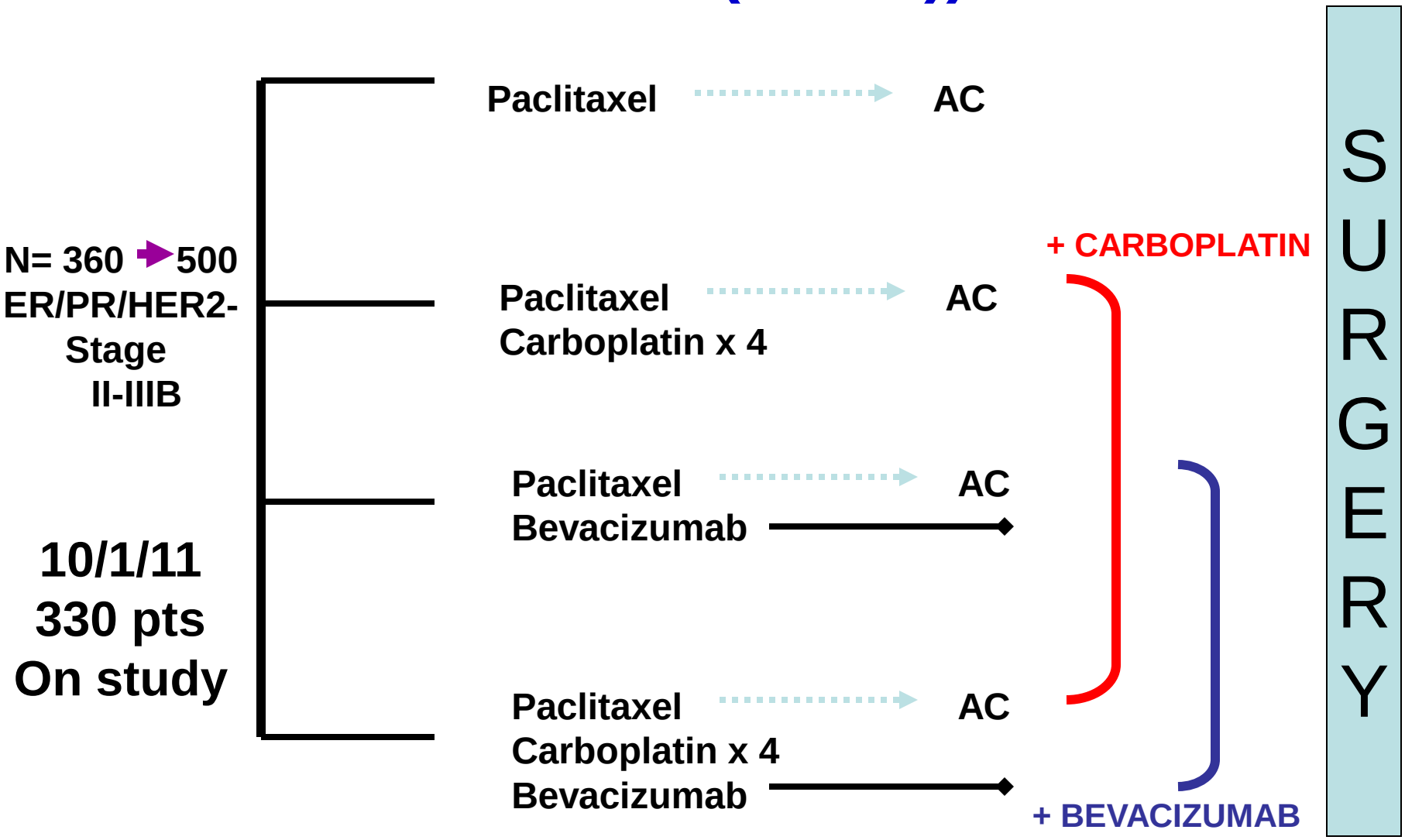
Predictors of Response to Neo-Adjuvant CDDP in TNBC





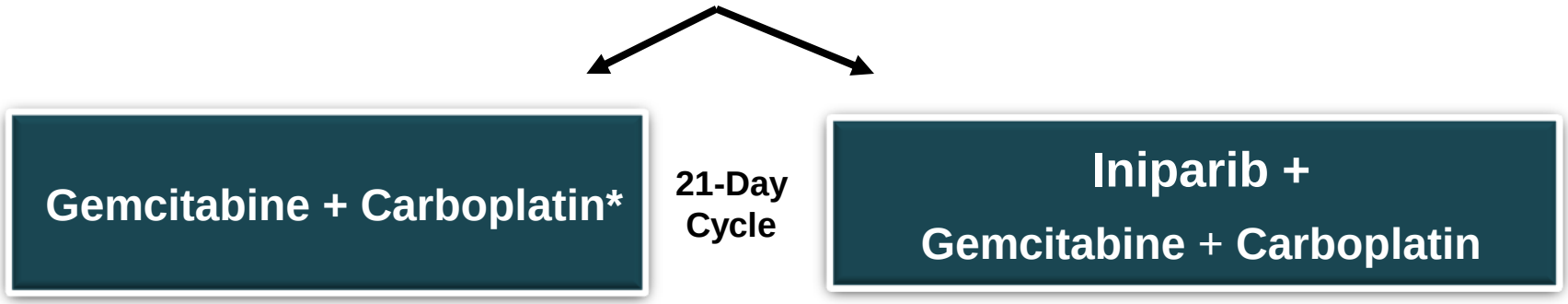
Silver D et al. JCO 2010

CALGB Triple Negative Neoadjuvant Trial Schema (40601))



Phase II Chemotherapy + Iniparib in Triple Negative Breast Cancer

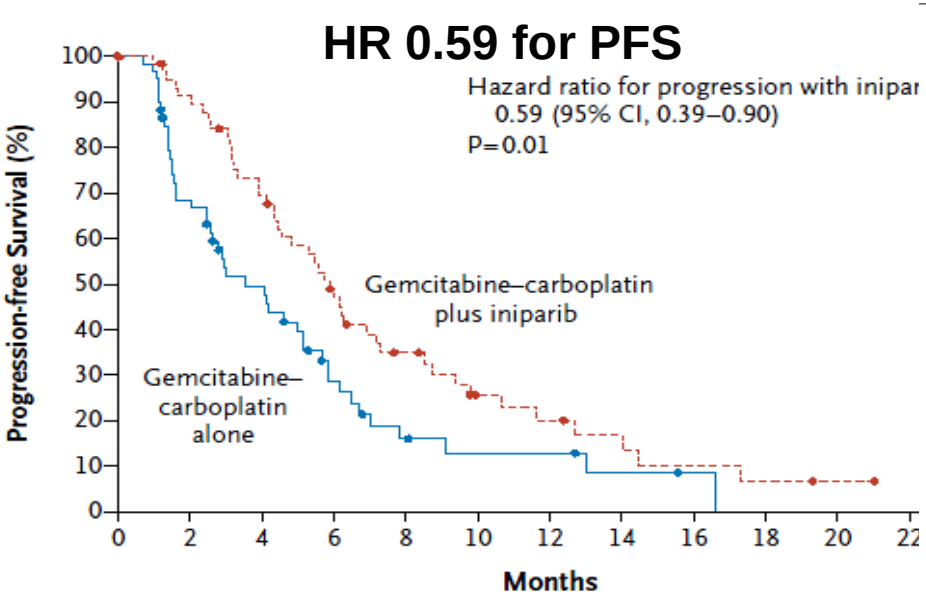
Metastatic triple negative
123 patients
No more than 2 prior chemo regimens
(except gemcitabine, platinum)

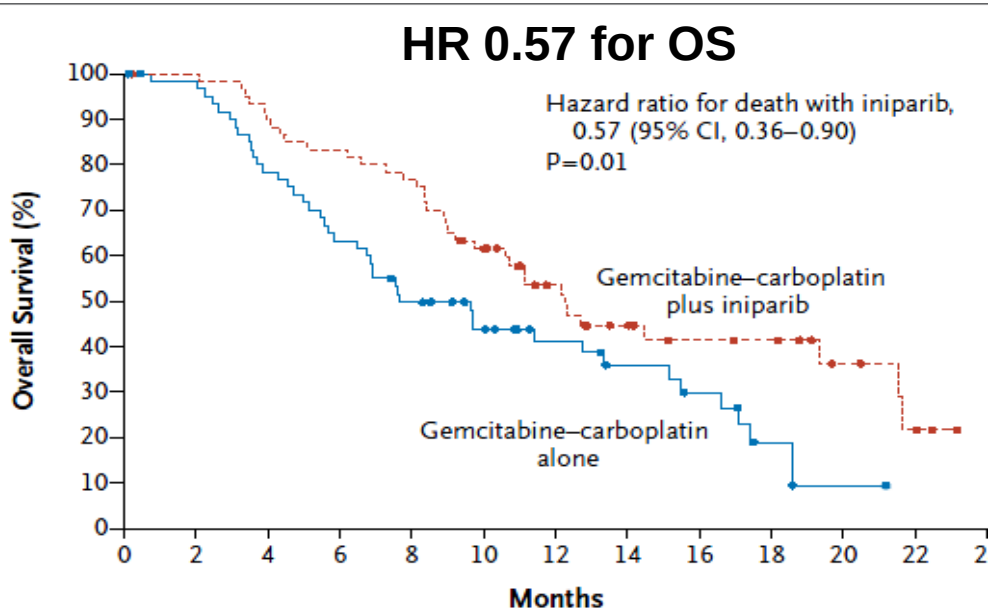


- **Primary goals: Clinical benefit rate, toxicity**
- **Secondary goals: Response, Progression-free and overall survival**

O'Shaughnessy et al, NEJM 2011

Randomized Phase II Gemcitabine/Carboplatin With Or Without Iniparib: Results

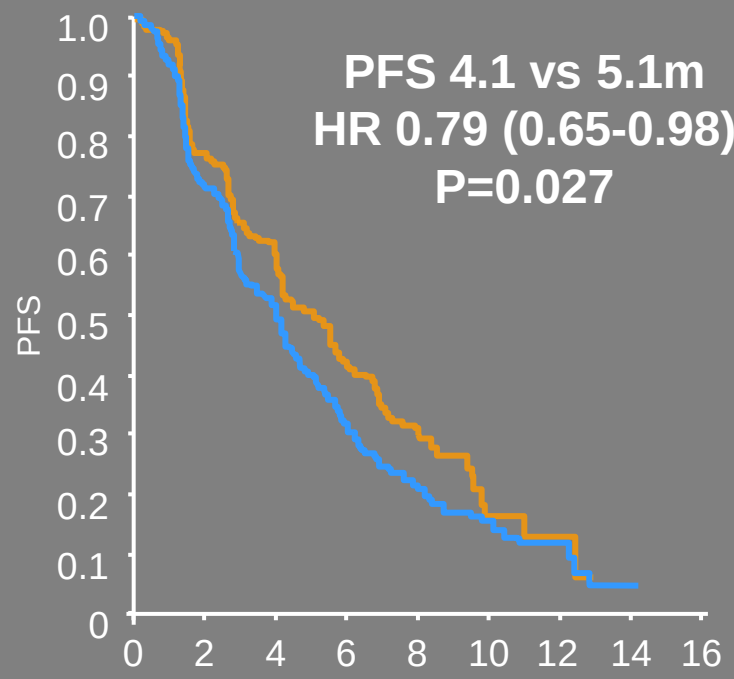


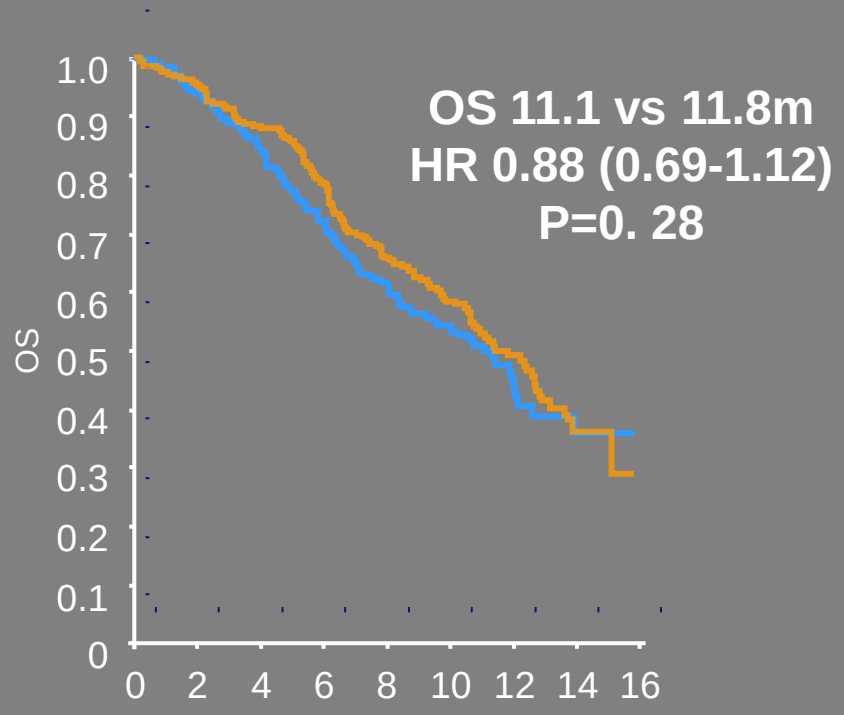


	GC (n = 62)	GC+I (n = 61)	*P*
Response	32%	52%	0.02
Clinical Benefit	34%	56%	0.01

O'Shaughnessy et al, NEJM 2011

Results of Phase III Trial

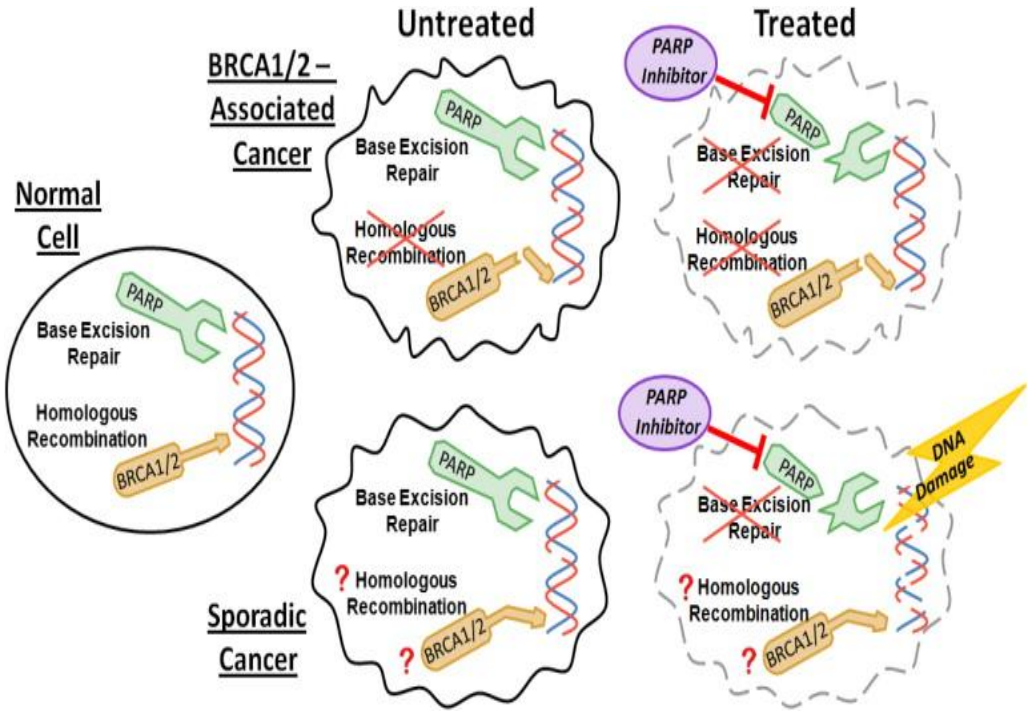




- **Primary statistical endpoints not met**
- **Numerical signal in favor of iniparib, but effect size small**
  - **If real, is 1 month advantage in PFS and < 1 month in OS clinically meaningful?**

O'Shaughnessy et al, ASCO 2011

PARP Inhibition in Breast Cancer



Ellisen Cancer Cell 2011

- Novel mechanism – inhibition of DNA damage repair
- Efficacy in BRCA-associated cancer

- Does this strategy work in non BRCA-associated tumors?
- Is iniparib a PARP inhibitor?
  - 1000x lower PARP inihibitory activity
  - Does not have additive toxicity (unlike others)
- What about other PARP inhibitors: veliparib or olaparib?
- To what extent is there cross resistance between PARP inhibitors and platinum

Appropriate Therapy for Triple Negative Disease

- High Risk (T2 and/or node positive)
  - AC-T dose dense
  - AC-T weekly
  - TAC
  - FEC-DOC
- Low Risk (T1N0)
  - AC
  - TC
  - CMF

Chemotherapy is effective for TNBC, and improvements in chemotherapy are worth pursuing in this settiing. New targets, and new targeted therapies are NEEDED.

Breast Cancer is a Family of Diseases

- At a minimum:
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  - ER + (luminal A)
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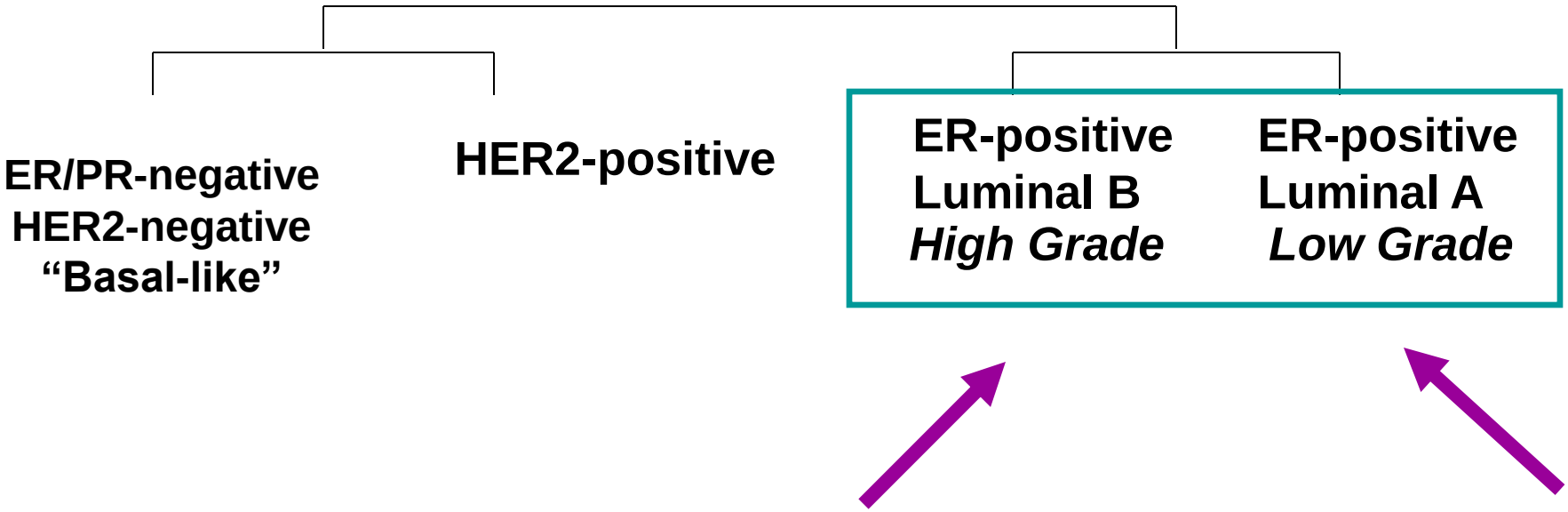
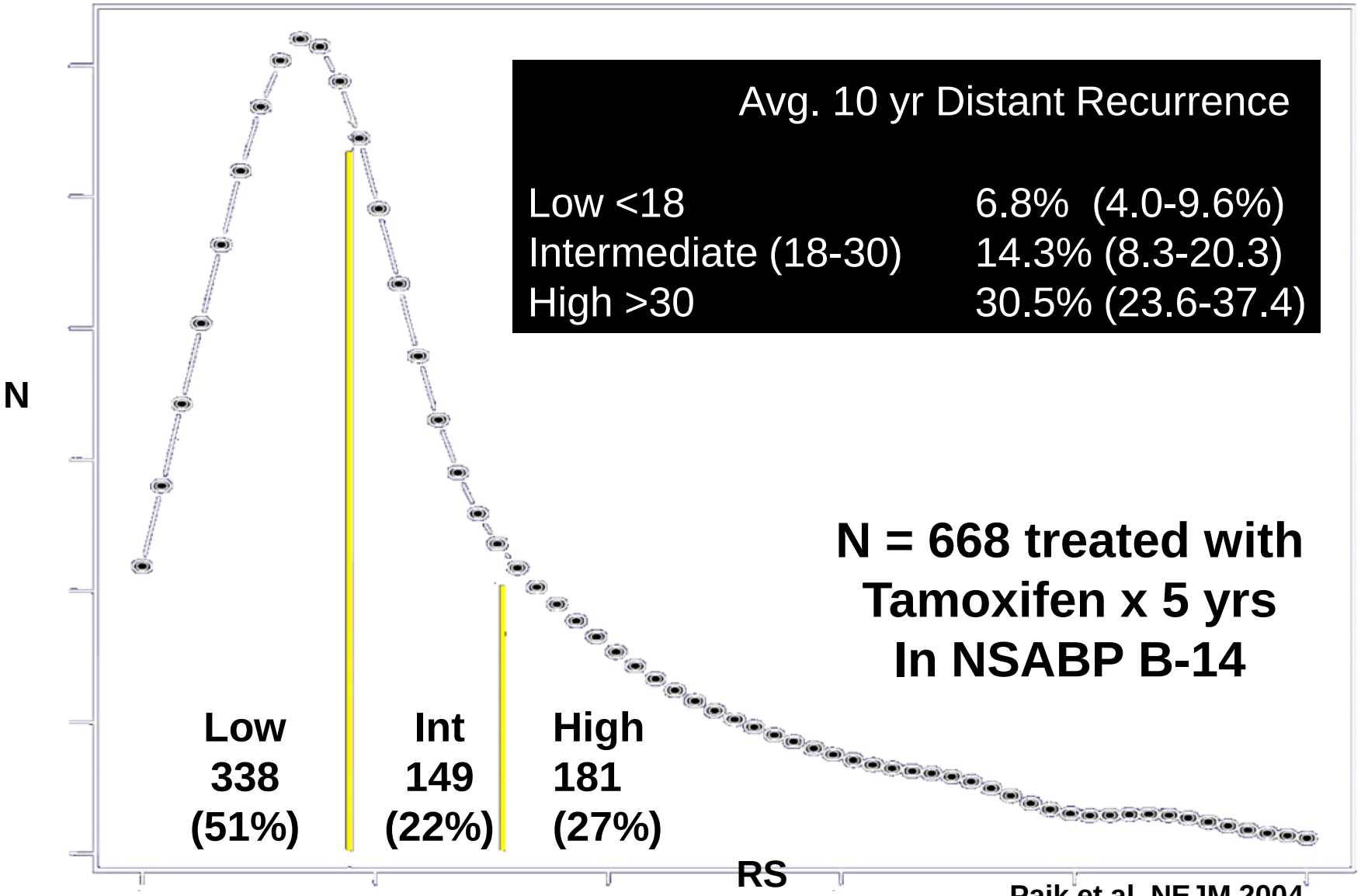


What Are The Best Treatments For HER2- Luminal Breast Cancer (ER+, PgR+/-, HER2-)?

1.Who needs chemotherapy?

2.How can we improve endocrine therapy?

Recurrence Score in Node Negative Patients Treated With Tamoxifen



Paik et al, NEJM 2004

Recurrence Score and Benefit from Chemotherapy in NSABP B-20

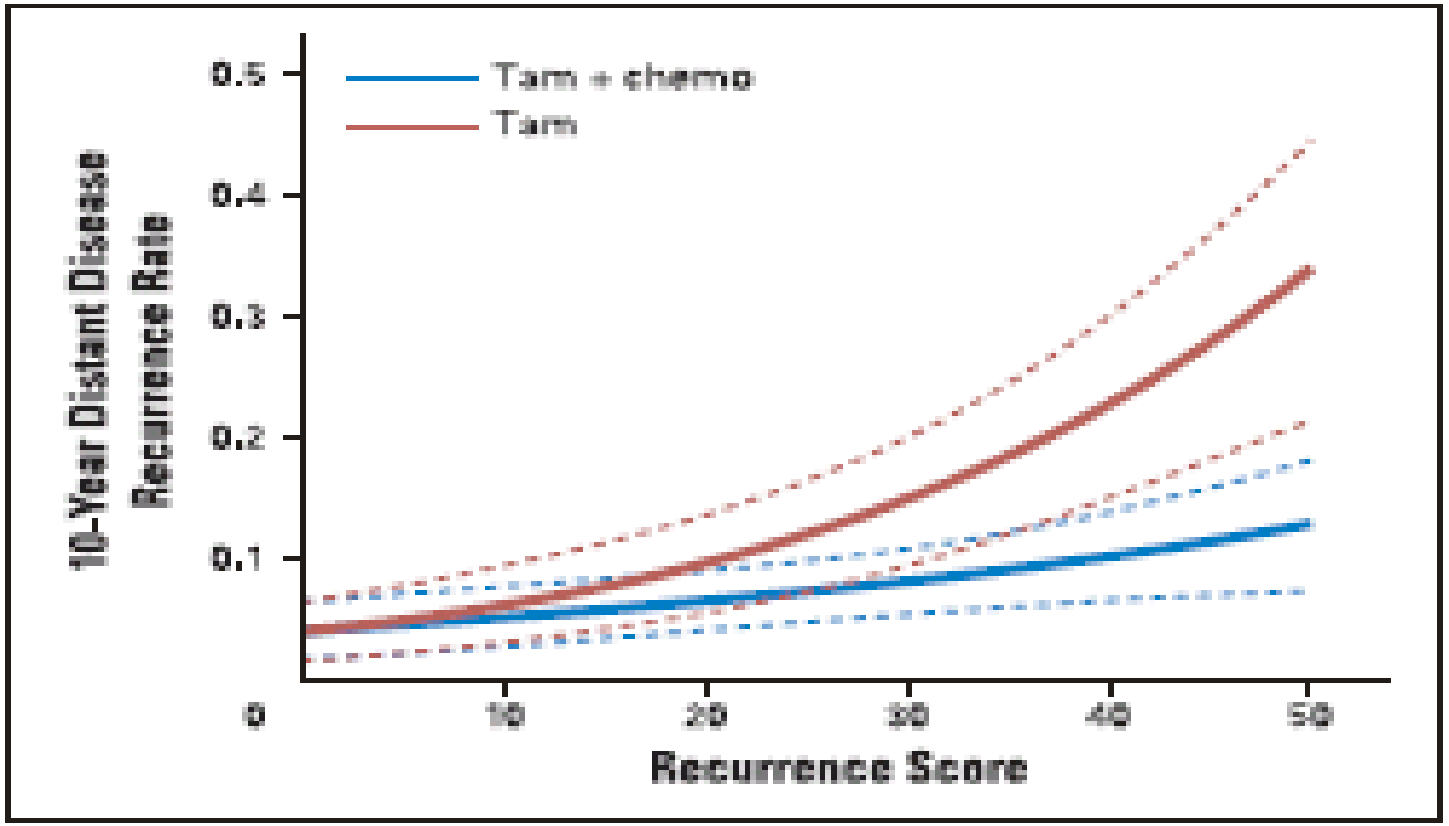
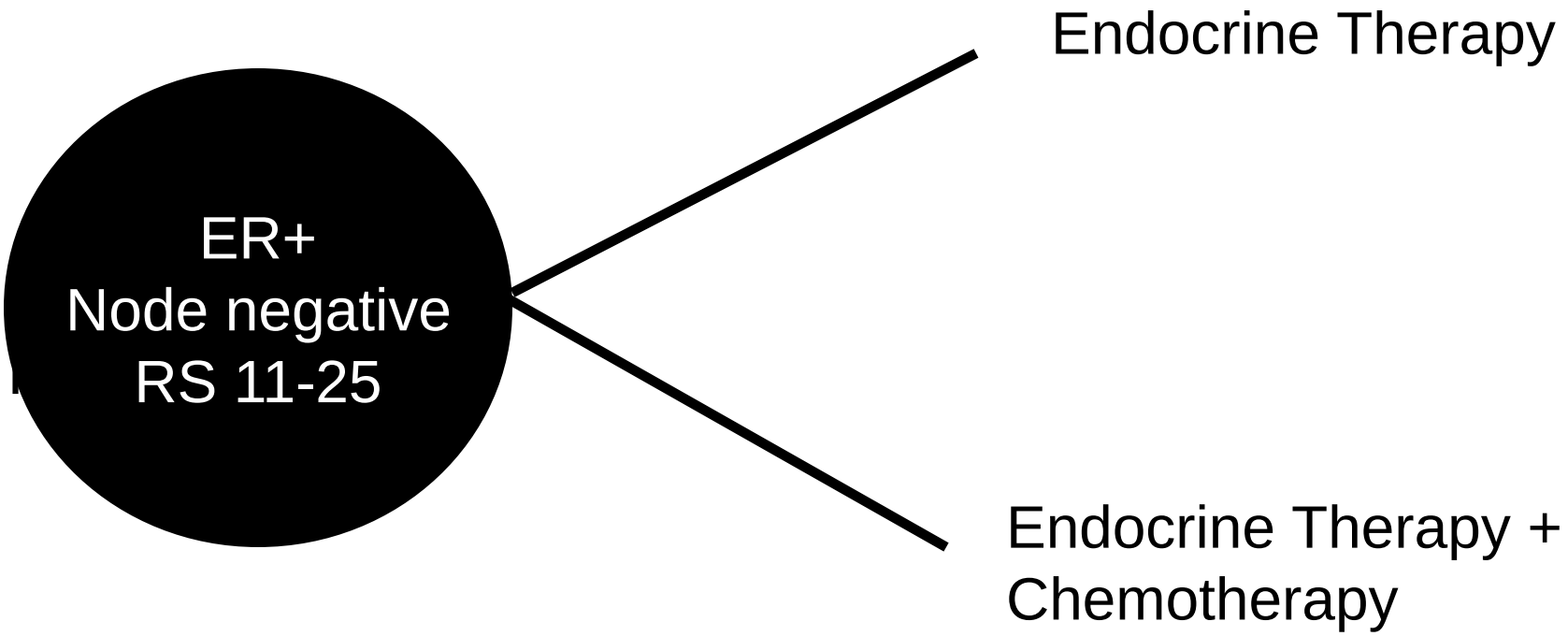


Fig 4. Linear fit of the likelihood of distant recurrence as a continuous function of recurrence score for the tamoxifen alone (TAM) and tamoxifen plus chemotherapy (TAM + chemo) treatment groups.

Paik et al, JCO2006

North American Intergroup TailorX Trial



PI: Joseph Sparano

S8814 CAFT vs T

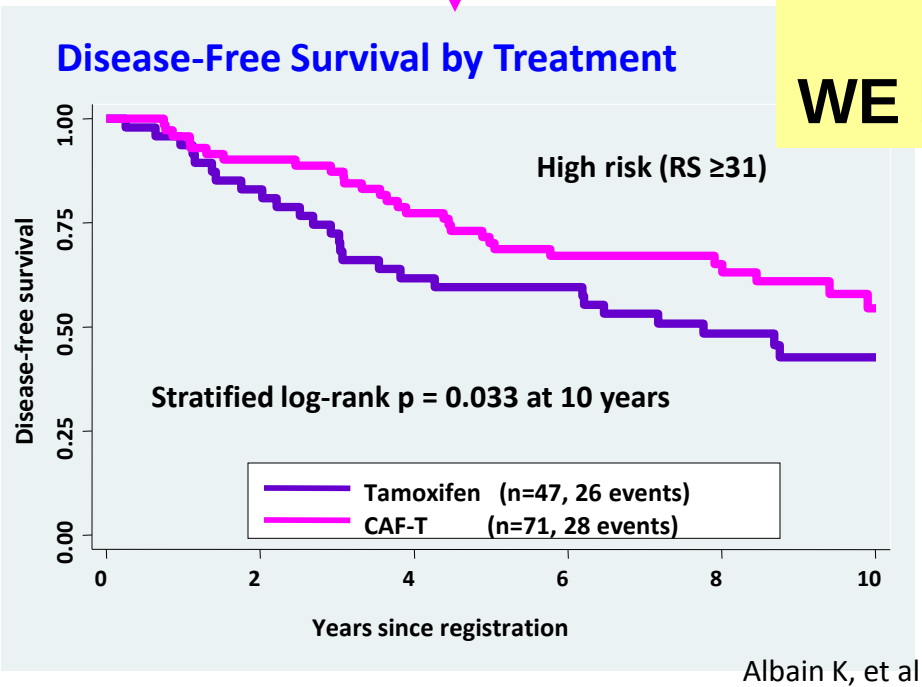
ER+ N+ Postmenopausal

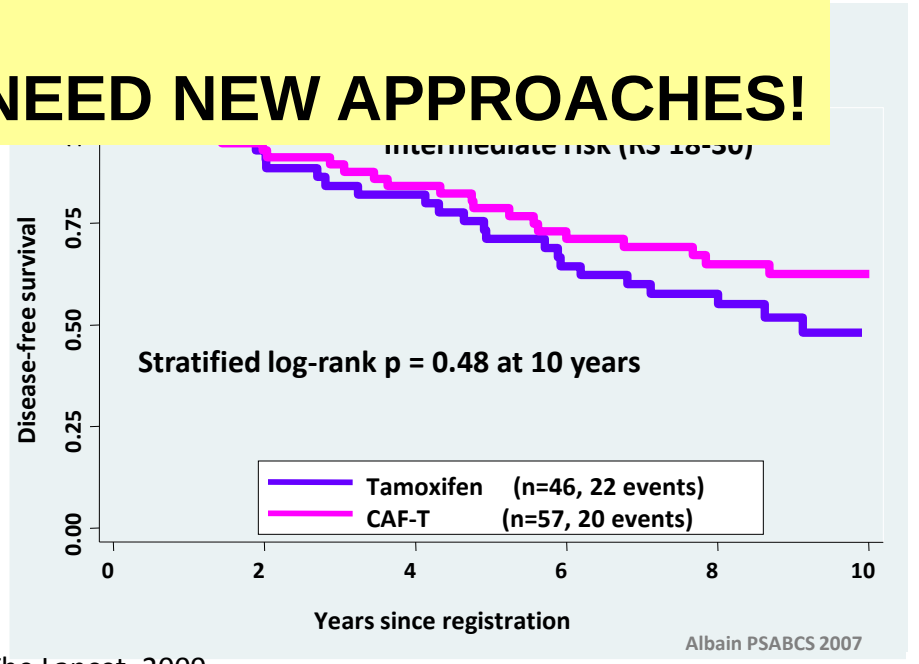
No benefit to CAF over time if low RS

Strong benefit if high RS

These patients have a high risk of disease recurrence with endocrine therapy alone, but this analysis would suggest that chemo is not the answer.

WE NEED NEW APPROACHES!





Albain K, et al The Lancet, 2009

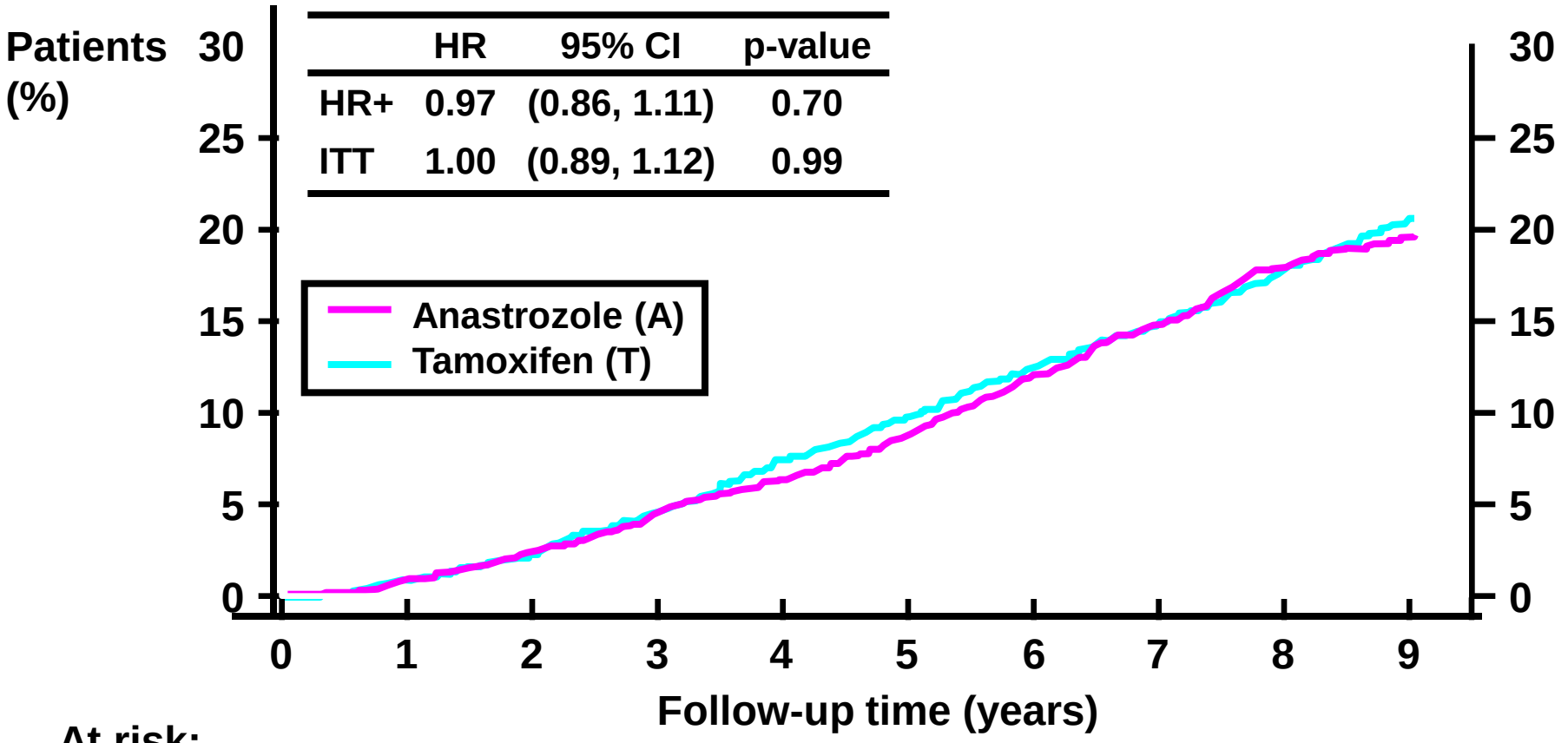
Which Patients with ER+ Disease Should Receive Chemotherapy (1)?

- **Lower levels of ER/PR**
- **High grade**
- **Higher Score on Oncotype or Poor Risk Signature on Mammoprint**
- **HER-2 Positive**
- **Higher absolute risk of recurrence irrespective of tumor biology (e.g. multiple positive nodes)**
- **?? Young age**

What About Endocrine Therapy?

- Premenopausal
  - 5 years of tamoxifen +/- ovarian suppression
- Postmenopausal
  - 5 years of therapy with AI alone or tam followed by an AI

ATAC 100 Month Follow-Up
Death: All Causes in HR+ Patients

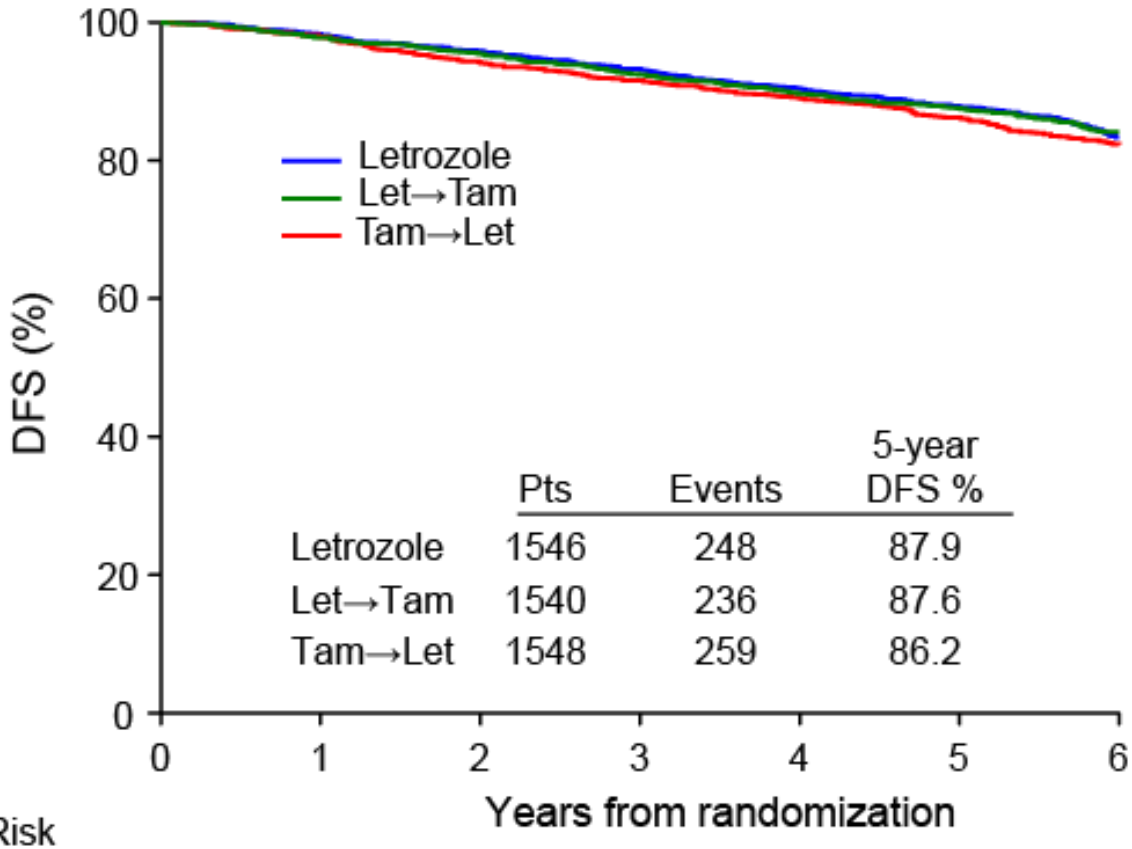


At risk:

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

Forbes et al SABCS 2007

BIG 1-98 Sequential Treatment
Disease-Free Survival

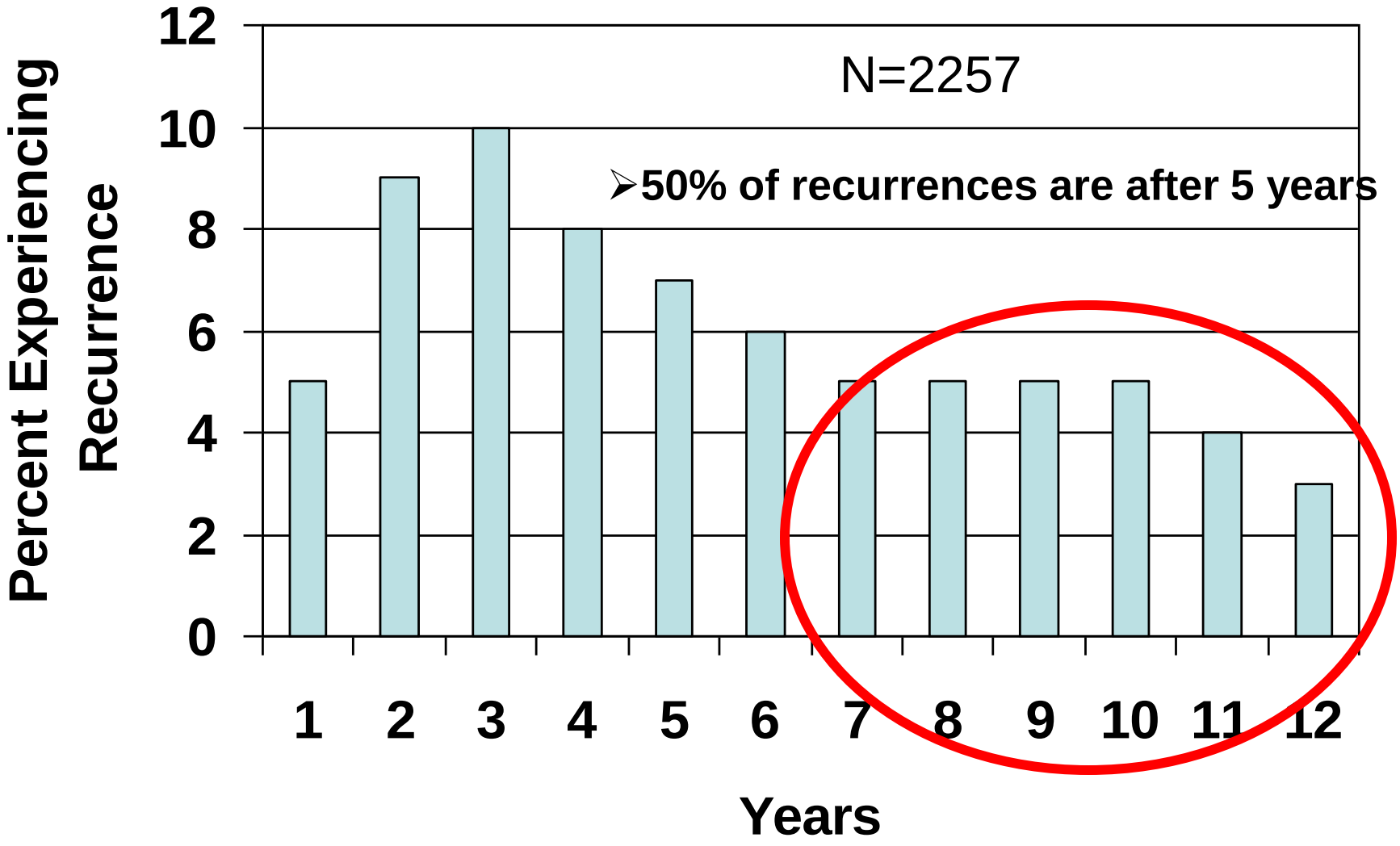


	Pts	Events	5-year DFS %
Letrozole	1546	248	87.9
Let→Tam	1540	236	87.6
Tam→Let	1548	259	86.2

Number at Risk				
Letrozole	1546	1470	1371	565
Let→Tam	1540	1467	1369	546
Tam→Let	1548	1457	1369	561

Mouridsen et al SABCS 2008

Annualized Hazard of Recurrence For ER+ Patients in ECOG Trials



Adapted from Saphner et al, JCO 1996

Different Risk Factors for Early and Late Recurrence in ER+ Disease?

EARLY RECURRENCE

- High grade
- Low ER receptor expression
- PgR negative
- HER-2 positive
- High recurrence score

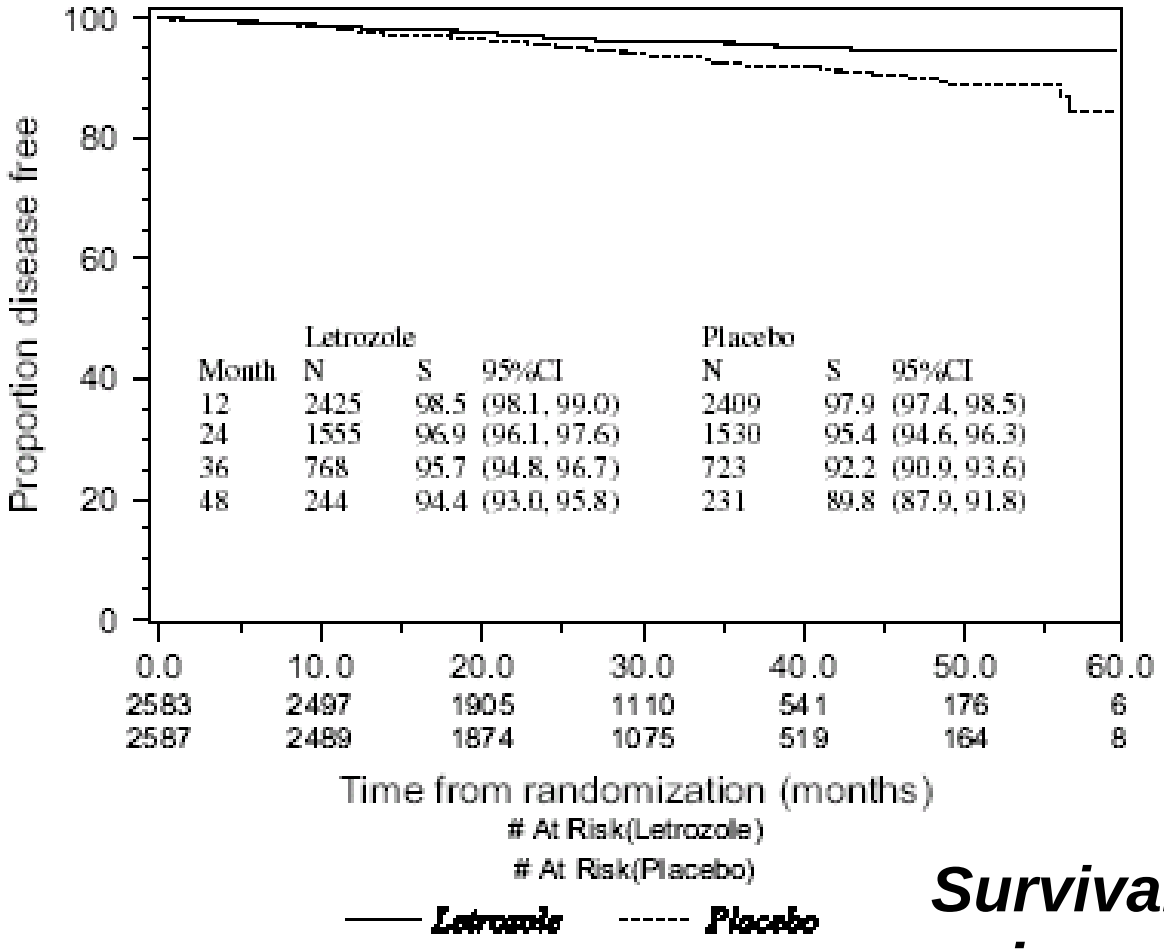
LATE RECURRENCE

- Low to intermediate grade
- High ER receptor expression
- PgR positive
- HER-2 negative
- Low recurrence score

- **High Disease Burden**
  - **-- Large Tumor**
  - **-- Multiple Positive Nodes**

- **High Disease Burden**
  - **-- Large Tumor**
  - **-- Multiple Positive Nodes**

Letrozole vs Placebo After TAM x 5 Years: MA-17 Disease-Free Survival



Median f/u 30 months

Letrozole 94.4%

Placebo 89.8%

P < 0.001

HR 0.58 (CI 0.45-0.76)

Survival advantage reported in node positive subset

Goss et al, JNCI 2005

Letrozole vs Placebo: Hazard Rates and Ratios Over Time (MA-17)

Months After Randomization	Hazard Rate (letrozole)	Hazard Rate (placebo)	Hazard Ratio (L vs P)
12	0.0093	0.0180	0.52 (0.40-0.64)
24	0.0105	0.0236	0.45 (0.33-0.56)
36	0.0090	0.0261	0.35 (0.21-0.48)
48	0.0059	0.0306	0.19 (0.04-0.34)

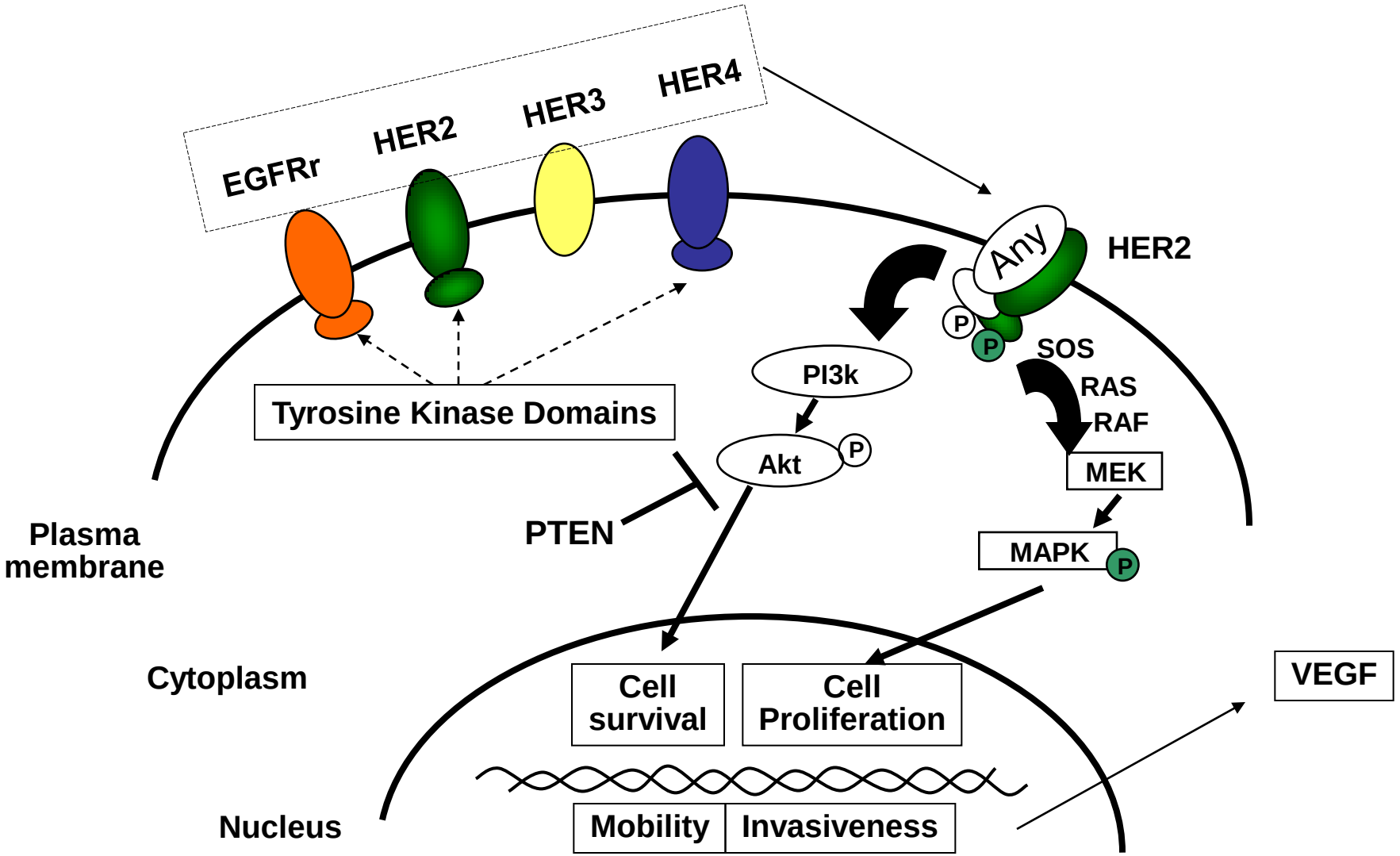
3% risk per year even at year 9

Ingle for MA20 investigators

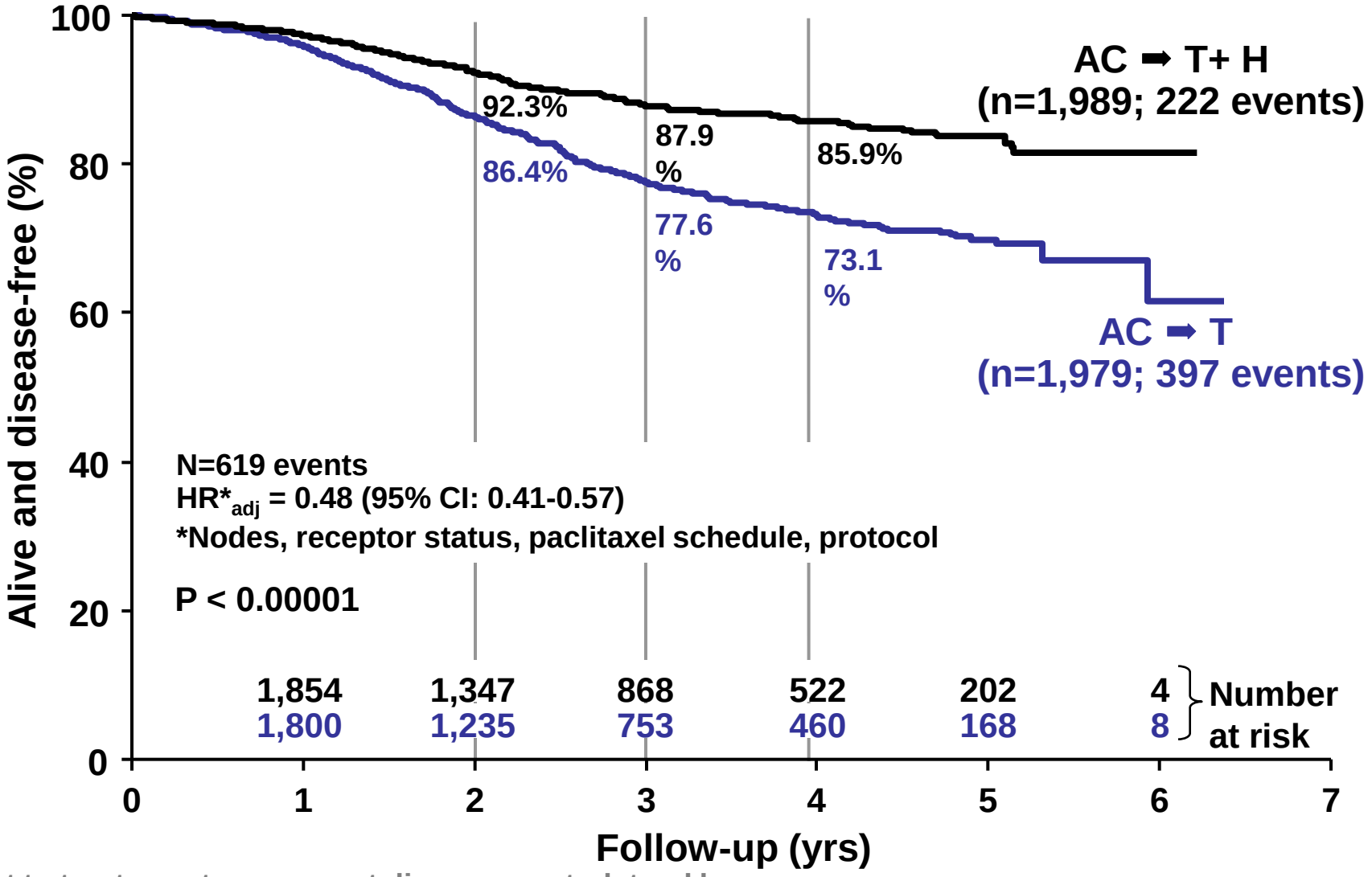
Prevention of Late Recurrence

- For many patients, prolonged therapy may be essential
- Drug resistance may be a problem, and continuing current agents indefinitely unlikely to be the answer
- Need molecular predictors of late recurrence, if they exist
- Is late recurrence a result of intrinsic tumor behavior, a change in the host, or both?

HER2 Signaling Pathways



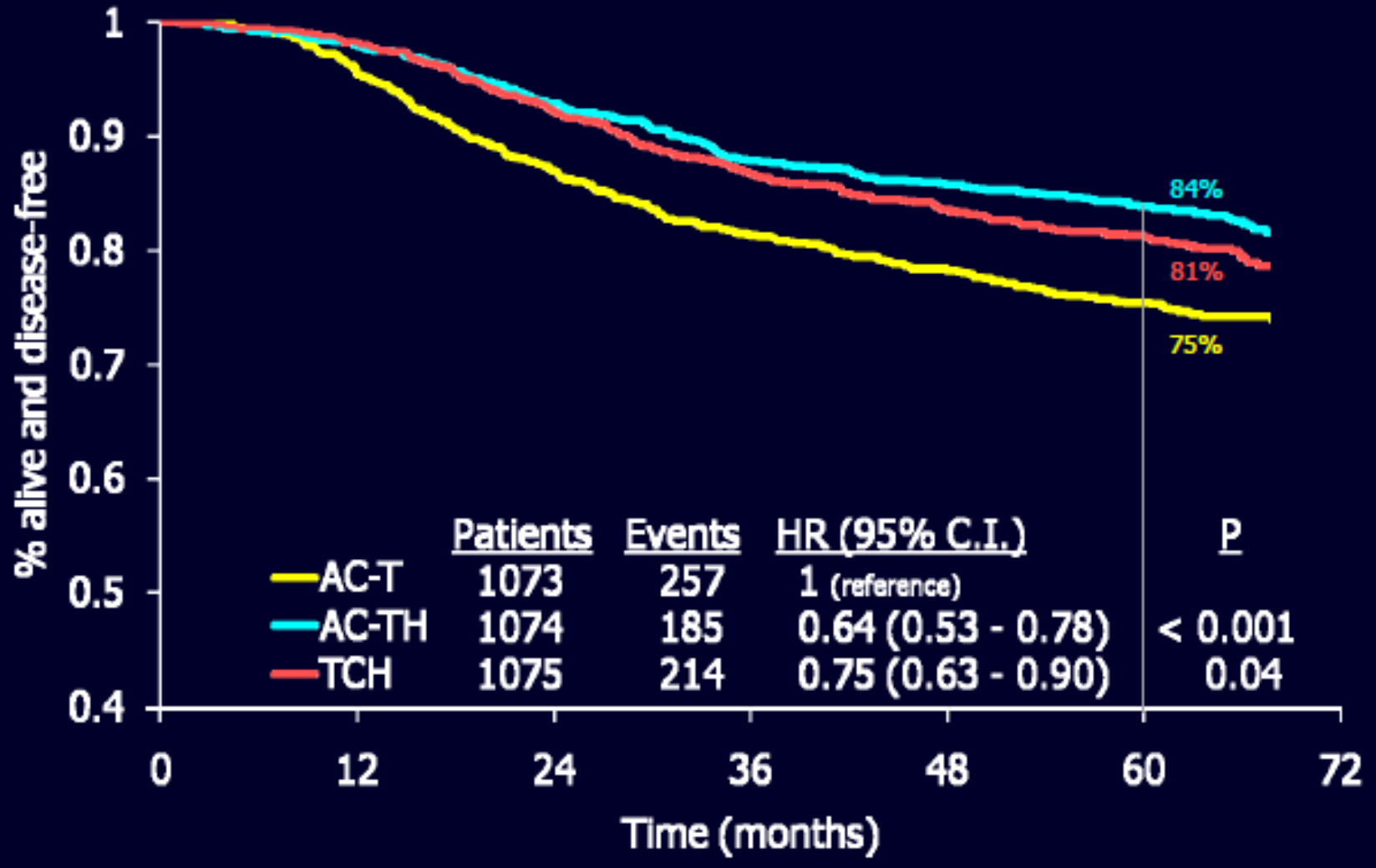
Updated N9831/B-31 Joint Analysis Disease-Free Survival*



*Intent to treat events: recurrent disease, contralateral bc, 2nd primary, death

Perez et al, ASCO 2007

Current BCIRG 006
Disease Free Survival – 3rd Planned Analysis



Slamon et al SABCS 2009 and NEJM 2011

What About Small Tumors (Less Than 1-2 cm) With Negative Nodes?

MD Anderson Series

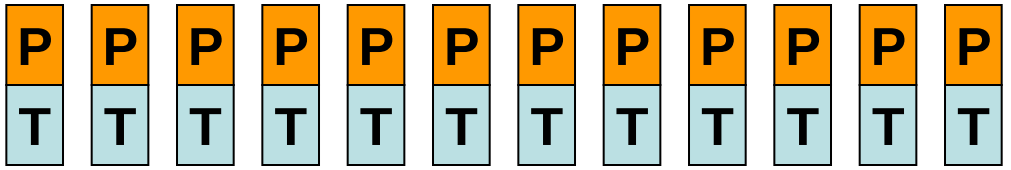
- 965 patients with T1a+b N0 tumors
- 10% were HER2+
- Median f/u 74 months with 72 recurrences
- 5-year DFS
  - 77.1% (HER2+) vs 93.7% (HER2-) P < 0.001
  - Multivariate HR 2.68 [1.44-5.0] P = 0.002
- 5-year DRFS
  - 84.4% (HER2+) vs 97.2% P < 0.001
  - Multivariate HR 5.3 [2.23-12.62] P < 0.001

Gonzalez A et al , JCO 2009

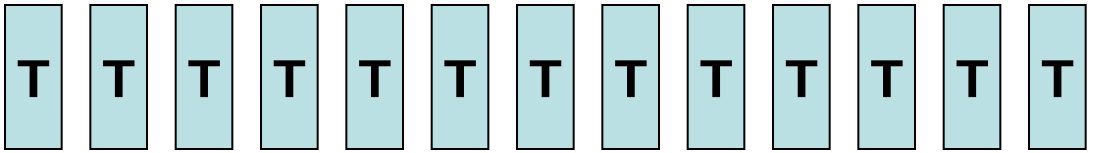
Completed DFCI Led Single Arm Multicenter Low Risk Trial

HER2+
ER+ or ER-
Node Negative
≤ 3 cm
PS 0-1
Adequate organ fx

Enroll →



12 WEEKS OF PACLITAXEL/TRASTUZUMAB



FOLLOWED BY 13 EVERY 3 WEEK DOSES OF TRASTUZUMAB

Results available in 2012-13

Agents Included In Ongoing And Planned Trials To Improve Outcomes

- Lapatinib → *Lapatinib + Trastuzumab*
- Bevacizumab – ongoing study of TCH +/- B
- Neratinib – ongoing study after trastuzumab based regimen
- Pertuzumab – trial planned
- T-DM1 – trial planned

With 85% DFS in patients with largely node positive disease, it will be hard to show substantial improvements in survival in overall population.

Not Everyone Needs More Therapy!

- **Who needs more?**
- **Who needs entirely different?**
- **Who needs less?**

The Challenge of Breast Cancer

- **Biologic subtypes are now well defined and new approaches need to be subtype specific**
- **Number of subtypes still unclear**
- **Heterogeneity within tumors is the norm**
- **Drug resistance is remarkably common**
- **Tumor dormancy is a major problem**
- **We can’t just develop the treatments, we have to be able to deliver them**