A Promising Future Therapeutic Strategy For Breast Cancer

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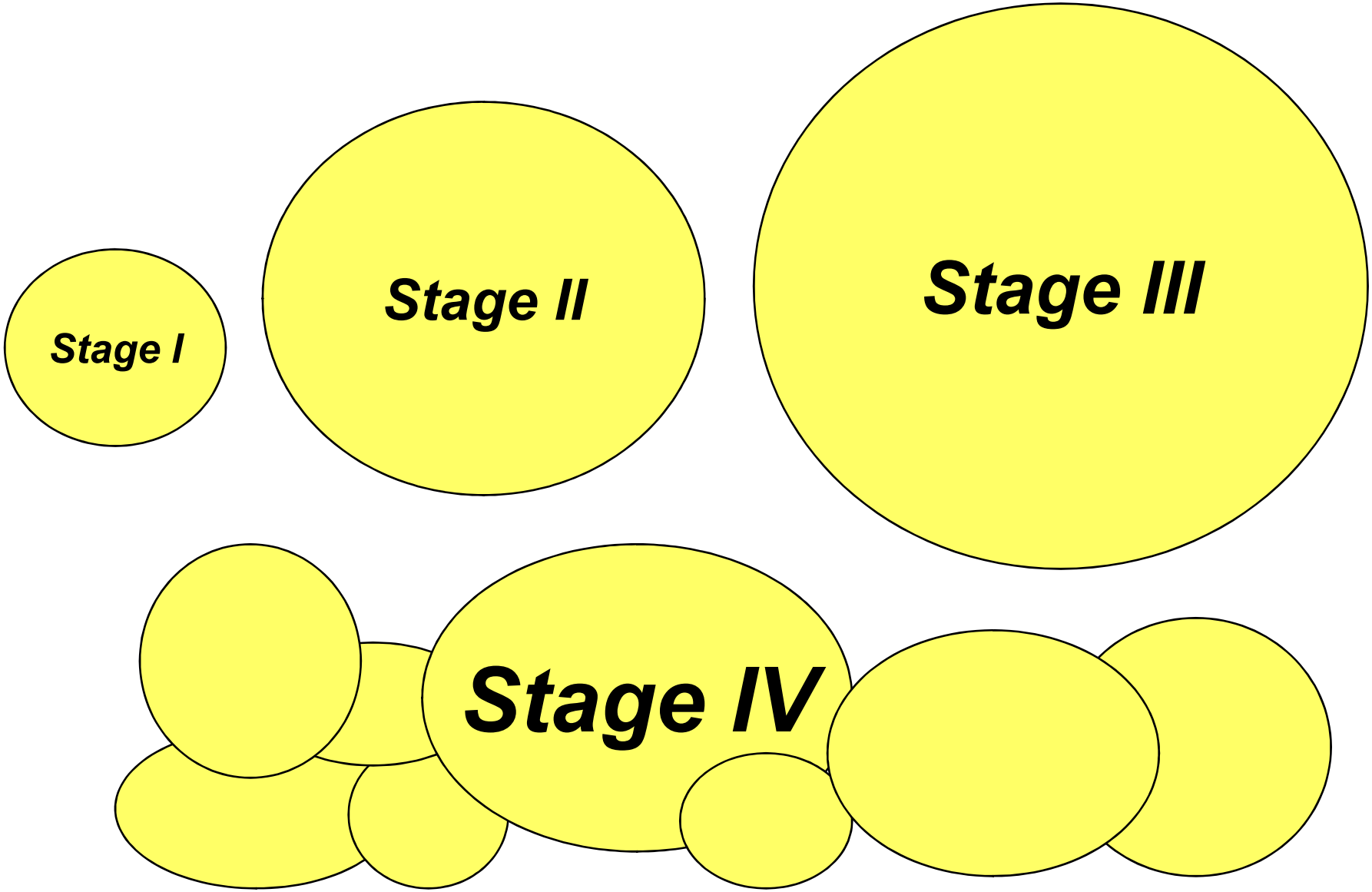
Breast Cancer:
As Conceived From 1980-2000+

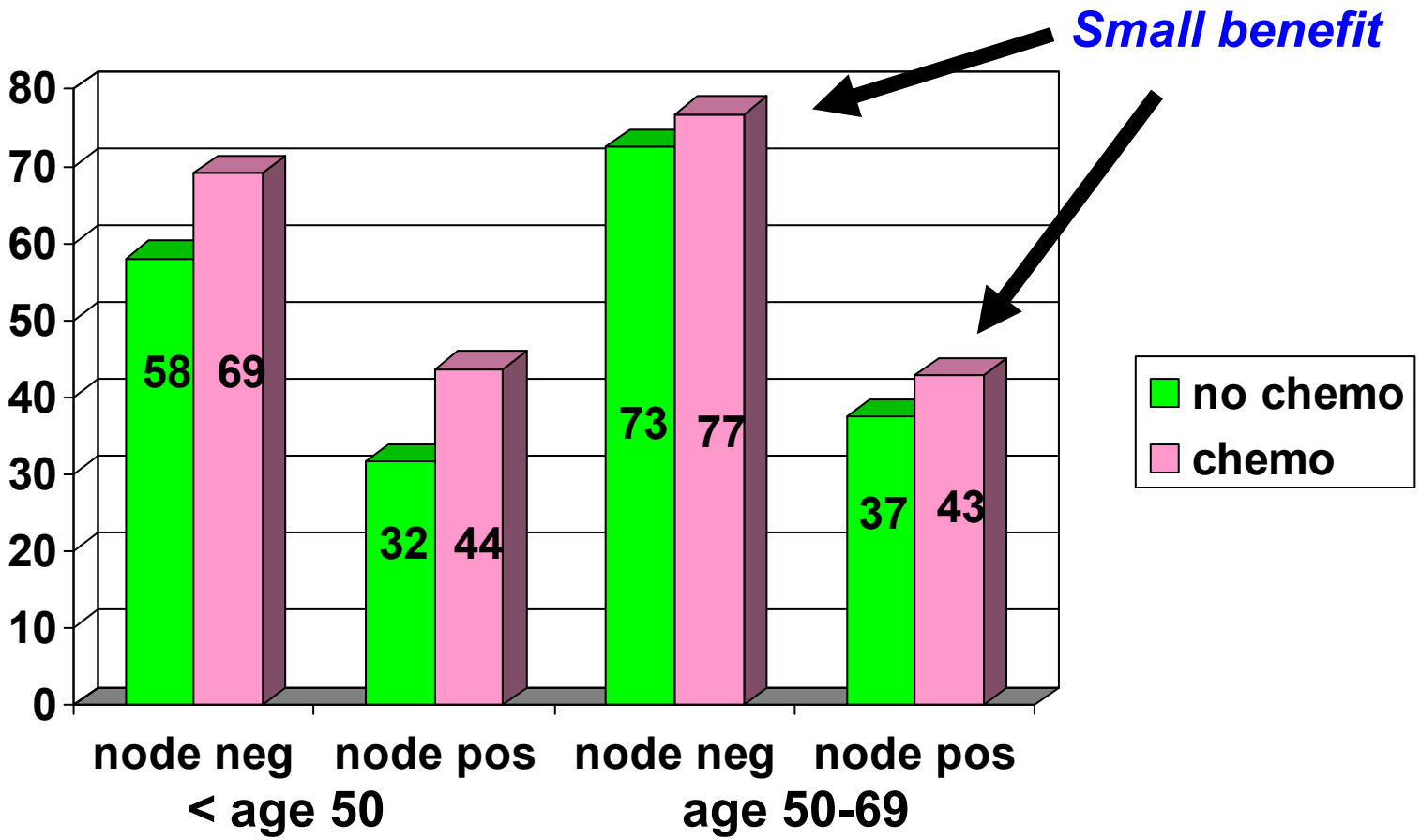


Breast Cancer: As Conceived From 1980-2000+

- We thought of breast cancer as a monolithic process
- While we recognized differences in size or disease burden, we did not acknowledge the biologic heterogeneity of the disease
- Our clinical trials tended to be inclusive of all patients with a given stage of disease
- Our treatments were “one approach works for all”

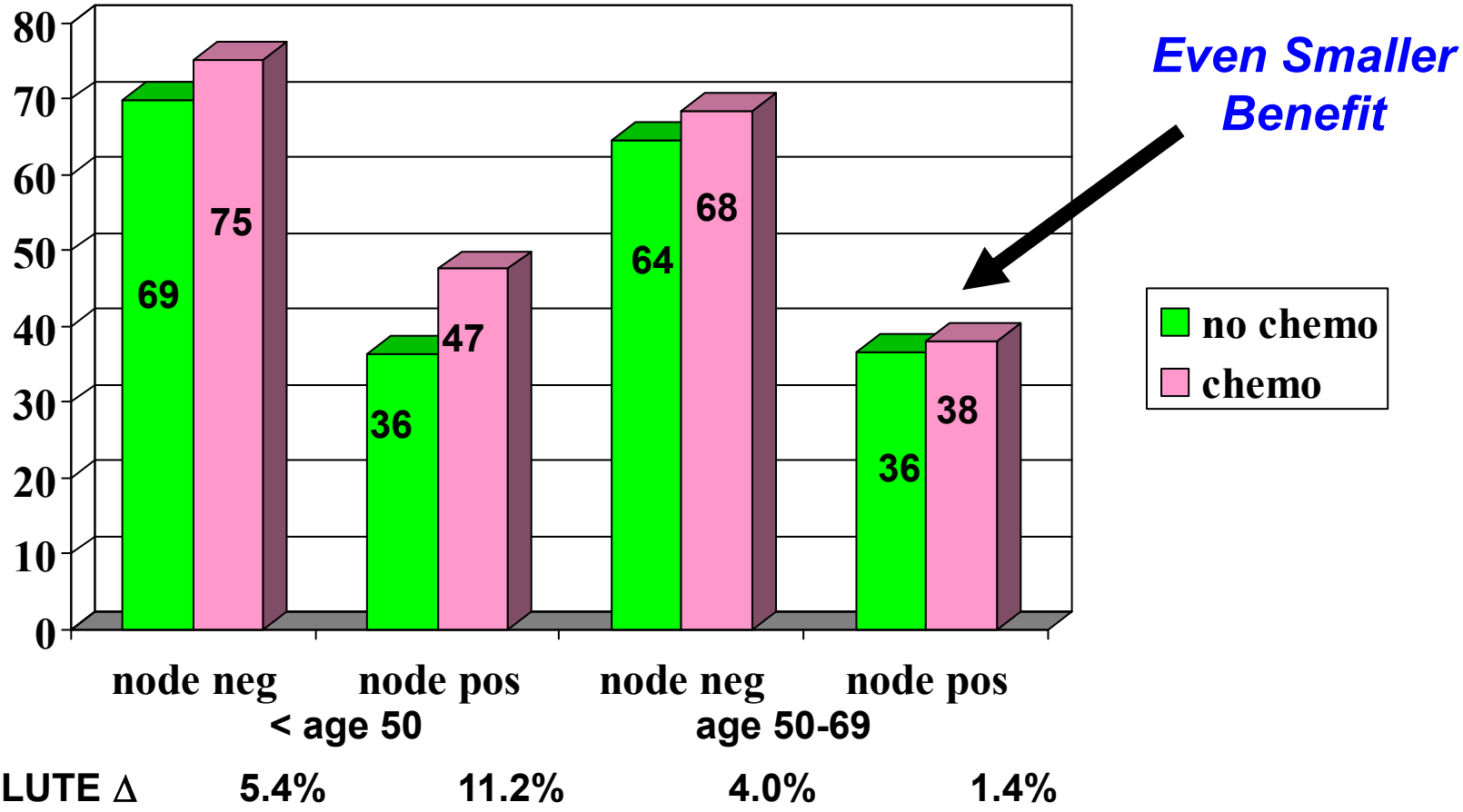
Polychemotherapy As Adjuvant Treatment: Oxford Overview 2000

DISEASE FREE SURVIVAL AT 15 YEARS F/U



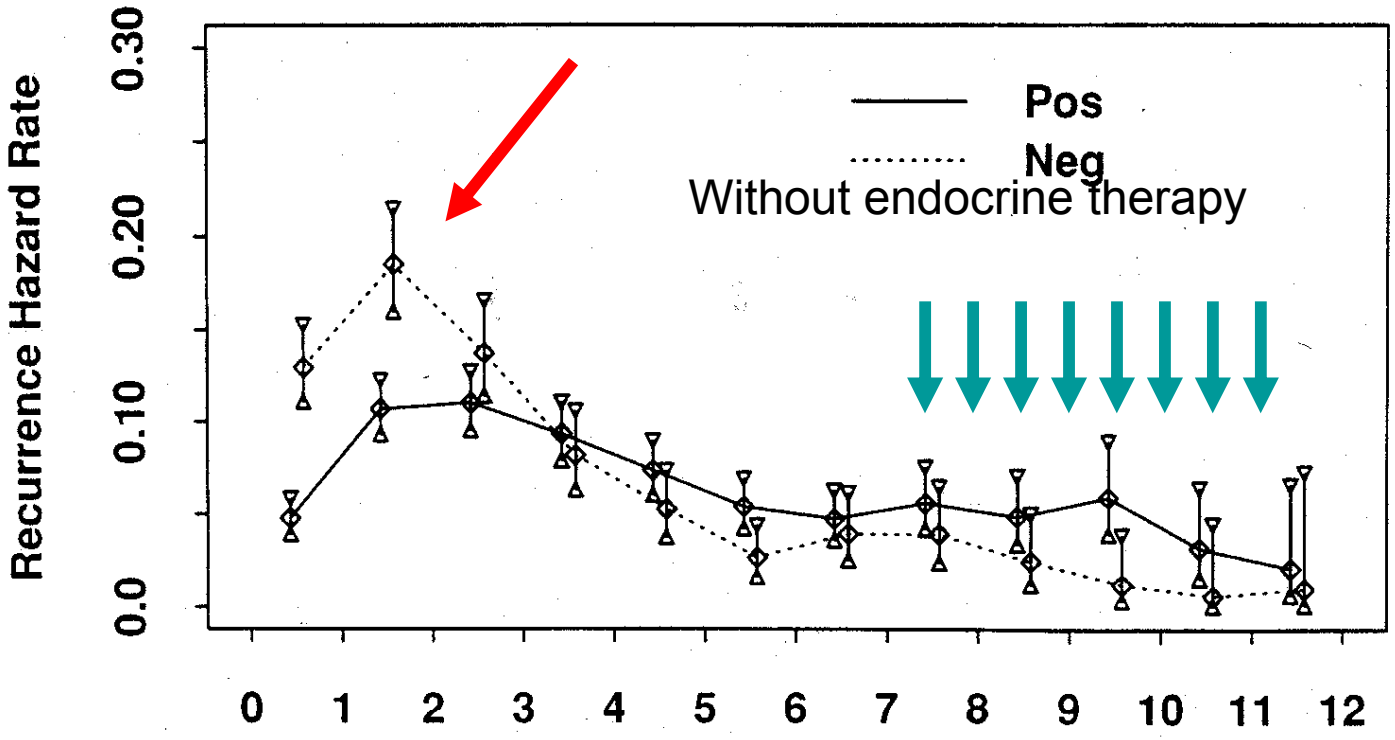
Polychemotherapy As Adjuvant Treatment: Oxford Overview 2000

OVERALL SURVIVAL AT 15 YEARS F/U



ABSOLUTE Δ	5.4%	11.2%	4.0%	1.4%

Risk of Recurrence After Breast Cancer Diagnosis By Hormone Receptor Status

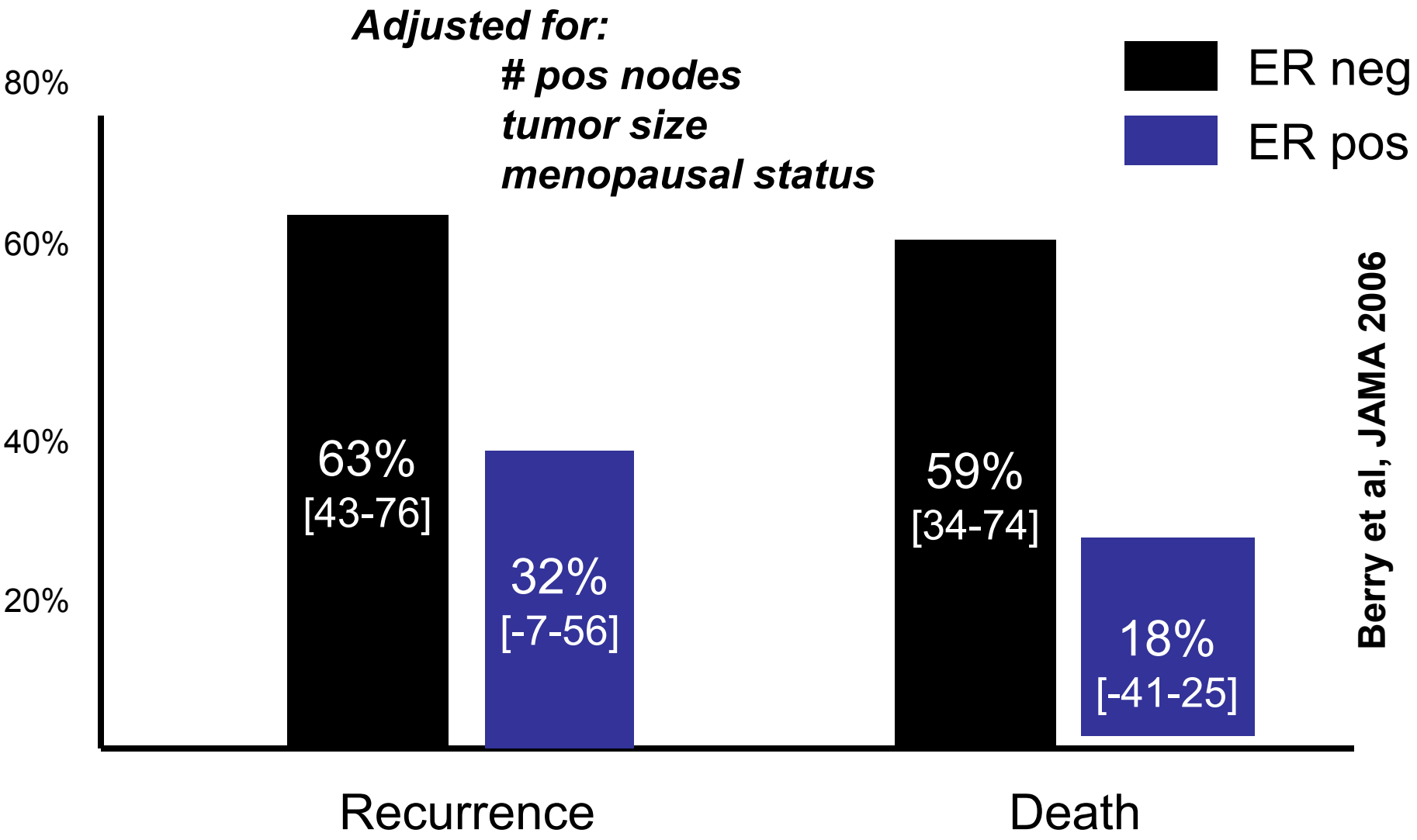


Number at Risk

Pos	2257	2096	1857	1642	1462	1313	1166	961	717	506	319	193
Neg	1305	1108	910	784	711	647	562	457	361	290	203	130

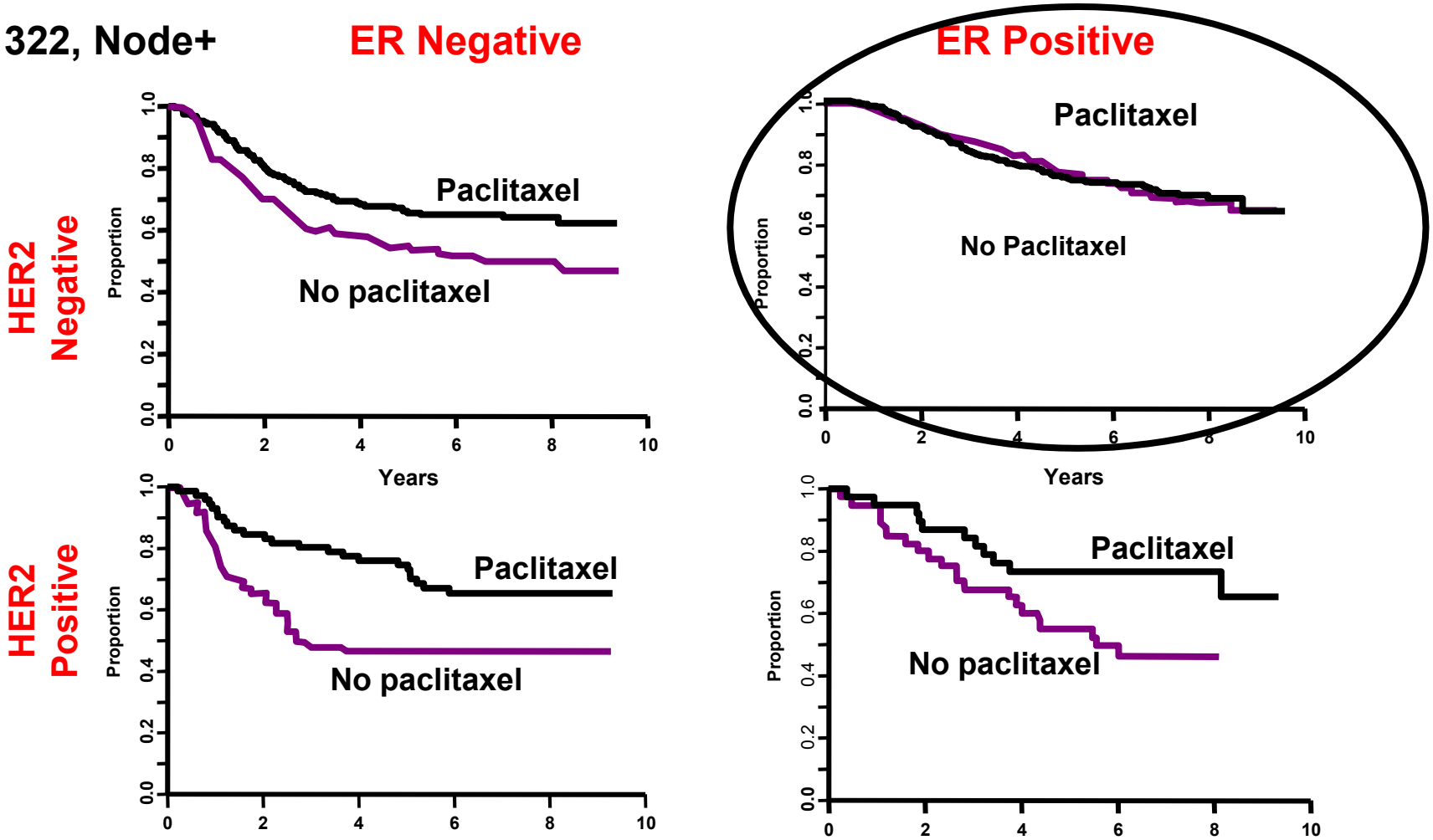
Saphner, et al. JCO 1996

CALGB Analysis: Unequal Benefits of "Modern Chemotherapy" By Hormone Receptor Status



CALGB 9344: HER2 Predicts AC-Paclitaxel Benefit
Exploratory DFS Analysis by Estrogen Receptor

n = 1322, Node+

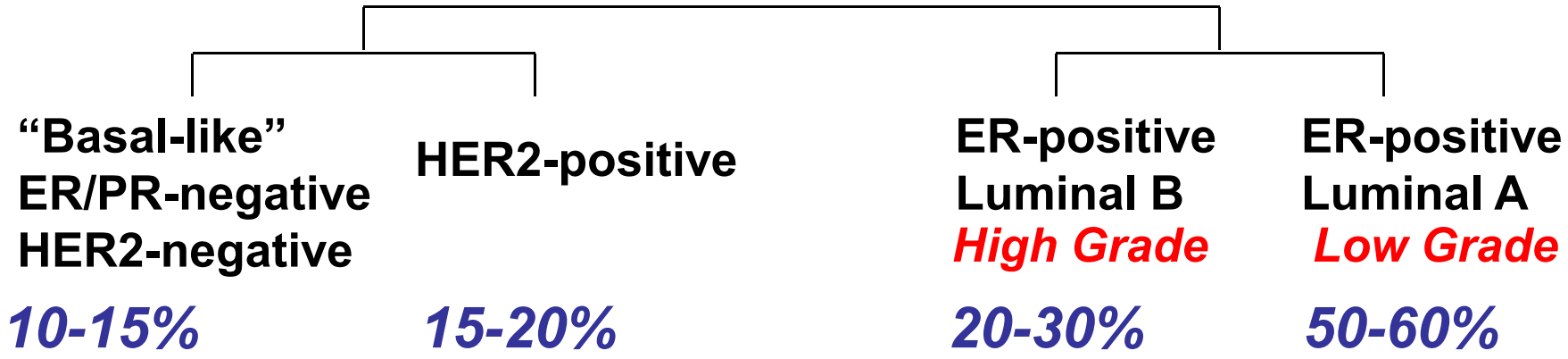


Benefit of taxane seen in HER2+ and Triple Negative Subsets

Hayes DF, et al. NEJM 2007

Breast Cancer is a Family of Diseases

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

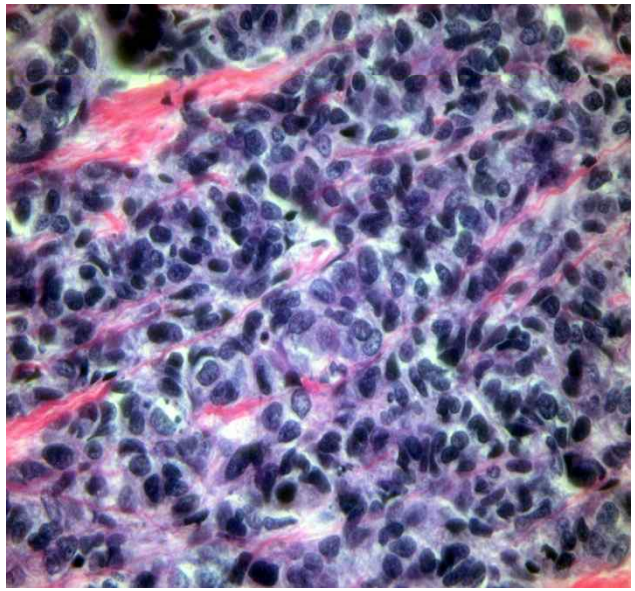


So How Do We Move Forward?

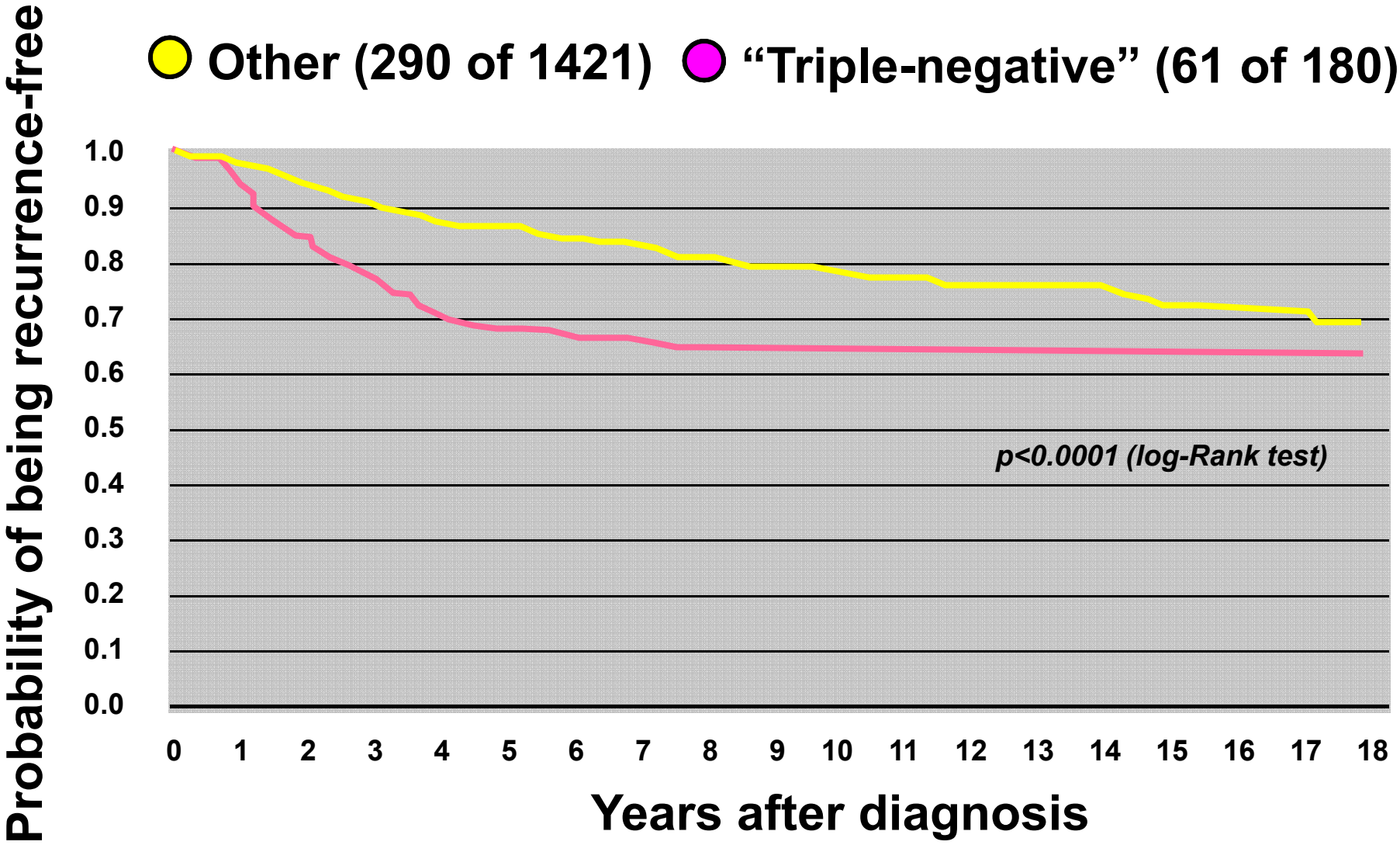
Step 1:
Divide and Conquer

Basal-like and/or Triple Negative Breast Cancer

- Unique subtype seen in gene array analyses accounting for 10-15% of all breast cancer; 85% of BRCA-/- breast cancer
- ER-, PgR-, and HER2-
- High grade
- Scant DCIS component
- Other characteristics
  - Mutations in p53 tumor suppressor gene
  - EGFR + (approximately 50%)
  - C-kit +
  - CK 5/6, 14, 17 + (basal cytokeritins)
  - High Ki67
- High degree of genomic instability

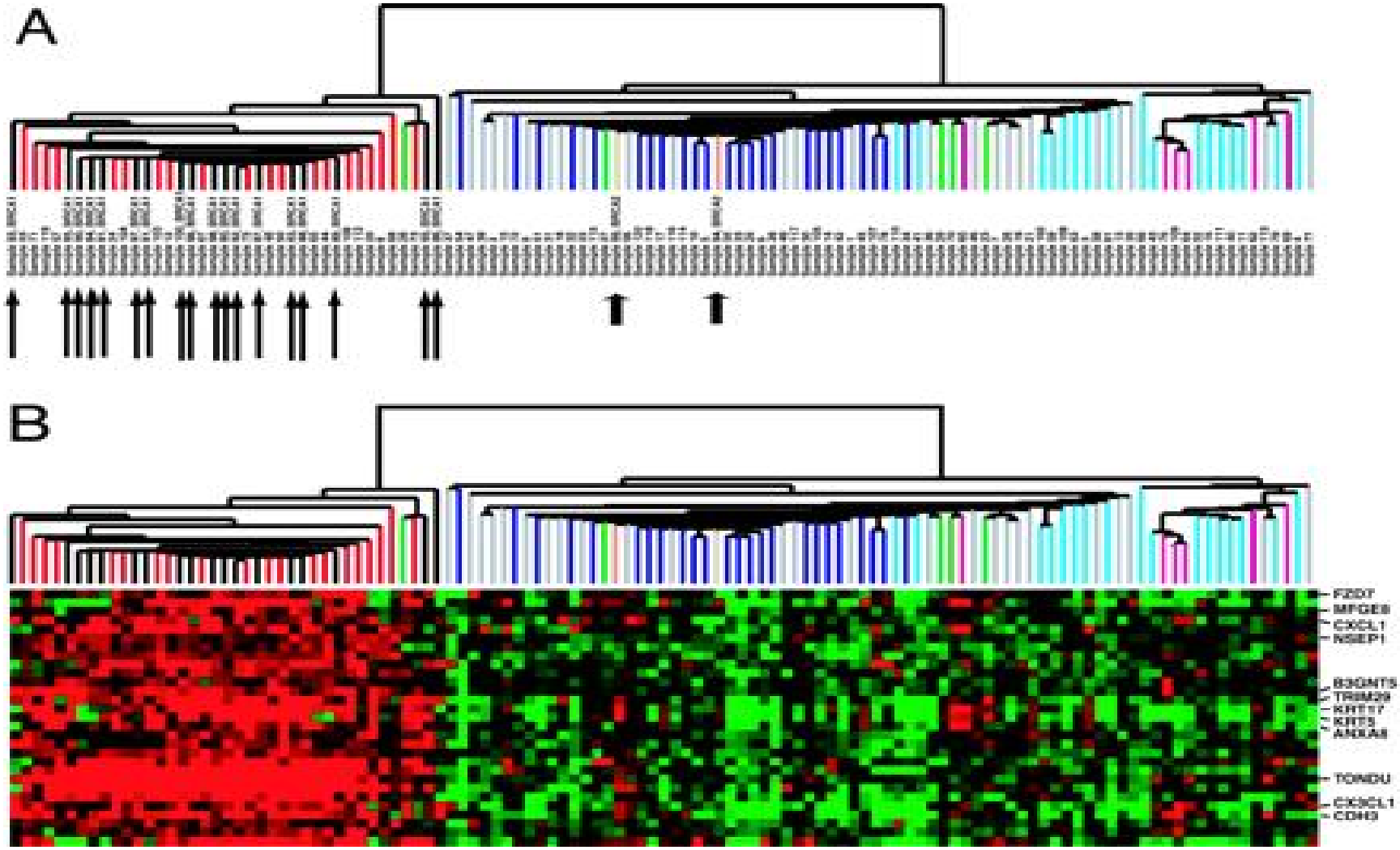


Henrietta Banting Breast Center
Distant Recurrence – F/U 8 years



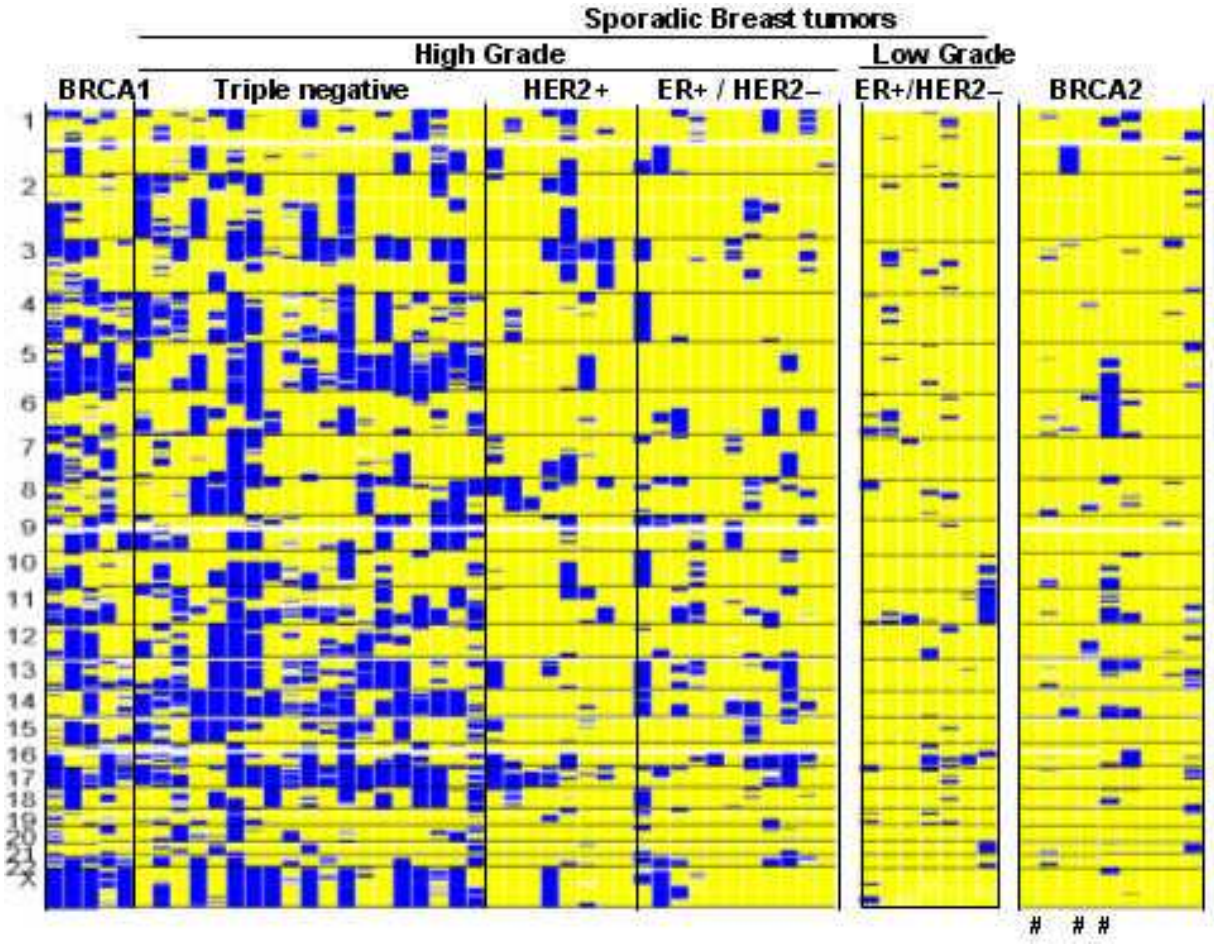
Dent, R. et al. Clin Cancer Res 2007;13:4429-4434

BRCA1-Tumors Are Basal-like



Sorlie T, PNAS, 2003;100:8418-20

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



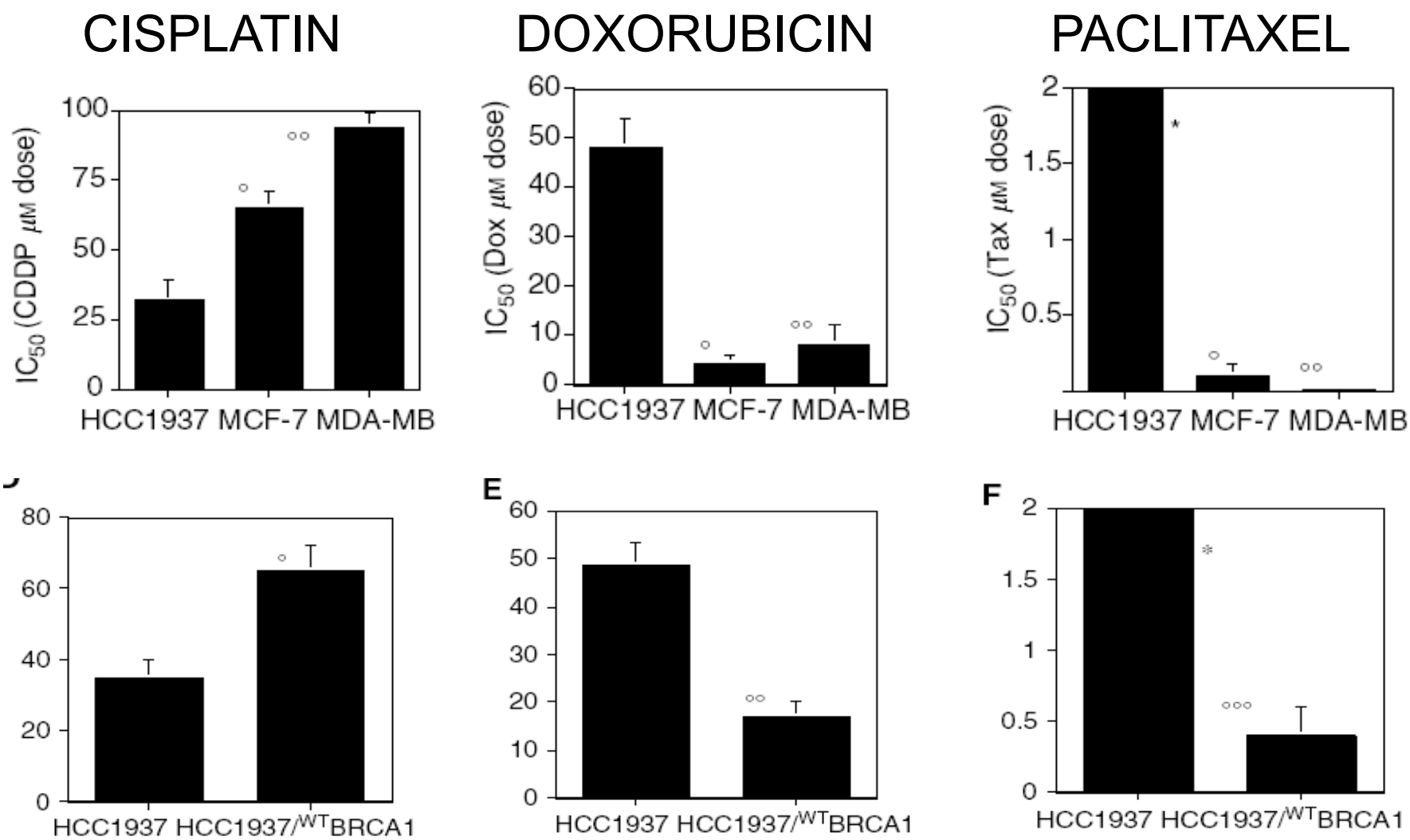
No allelic loss (heterozygosity intact)

Allelic loss (LOH)

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

Silver, Wang, Richardson, Iglehart: personal communication

BRCA1-Deficient Cells Are Hypersensitive to Cisplatin



Tassone et al, 2003 BJC

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%)

Predictors of Response:

- **Young age**
- **BRCA 1 mutation (2/2)**
- **BRCA1 methylation**

Silver et al, in press, Journal of Clinical Oncology

Cisplatin As Preoperative Therapy For Patients With BRCA1 Mutations

- 25 patients with BRCA1 mutations
- Stage I-III disease
  - 10 T1 tumors
  - 18 clinically N
- Treatm
  - 75 mg/m^2 q 3 weeks x 4
  - +
- Path CR = No invasive tumor in breast or nodes

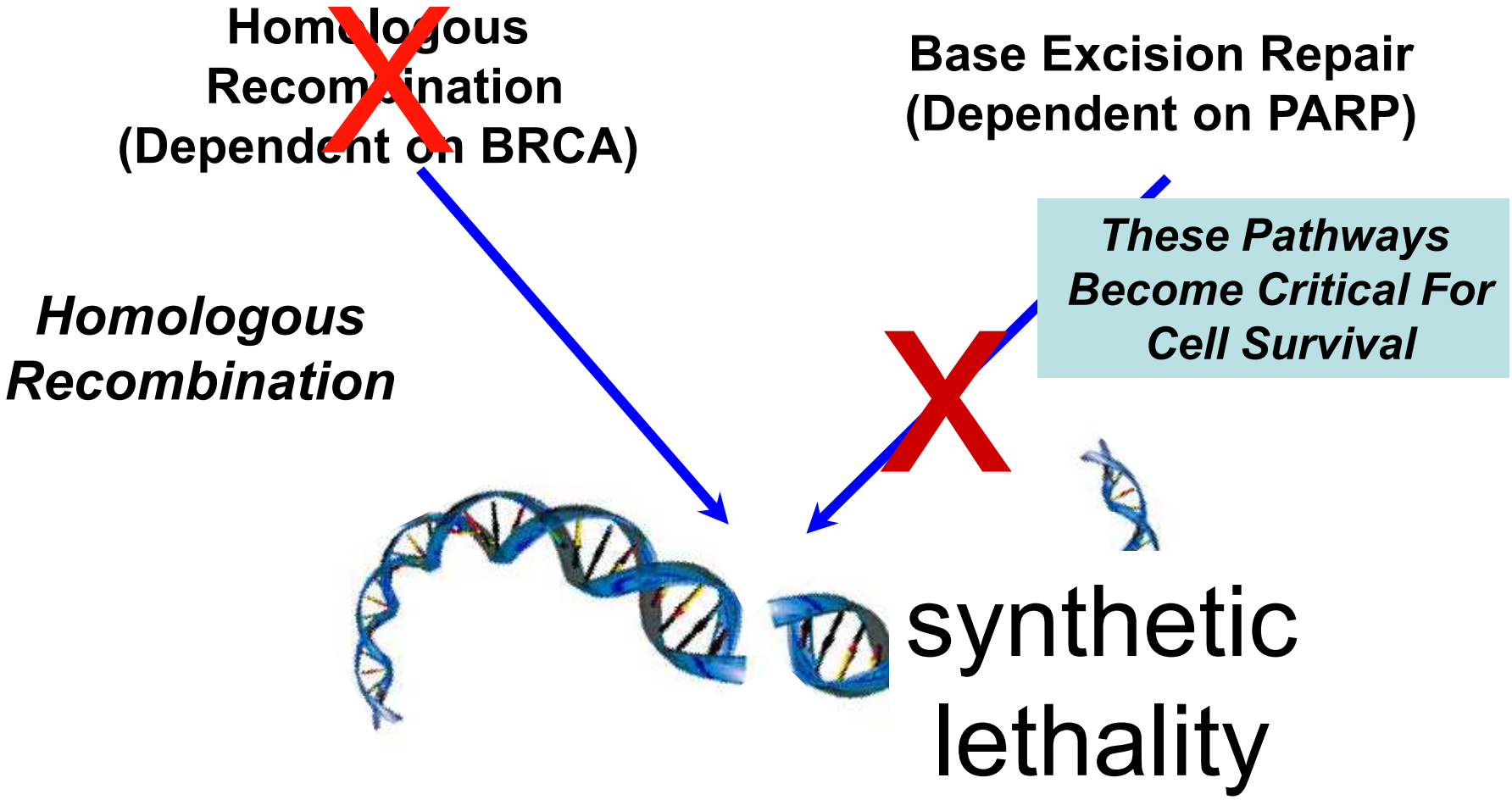
Complete Pathologic Response
18/25 = 72%

Gronwold/Byrski et al, ASCO 2009

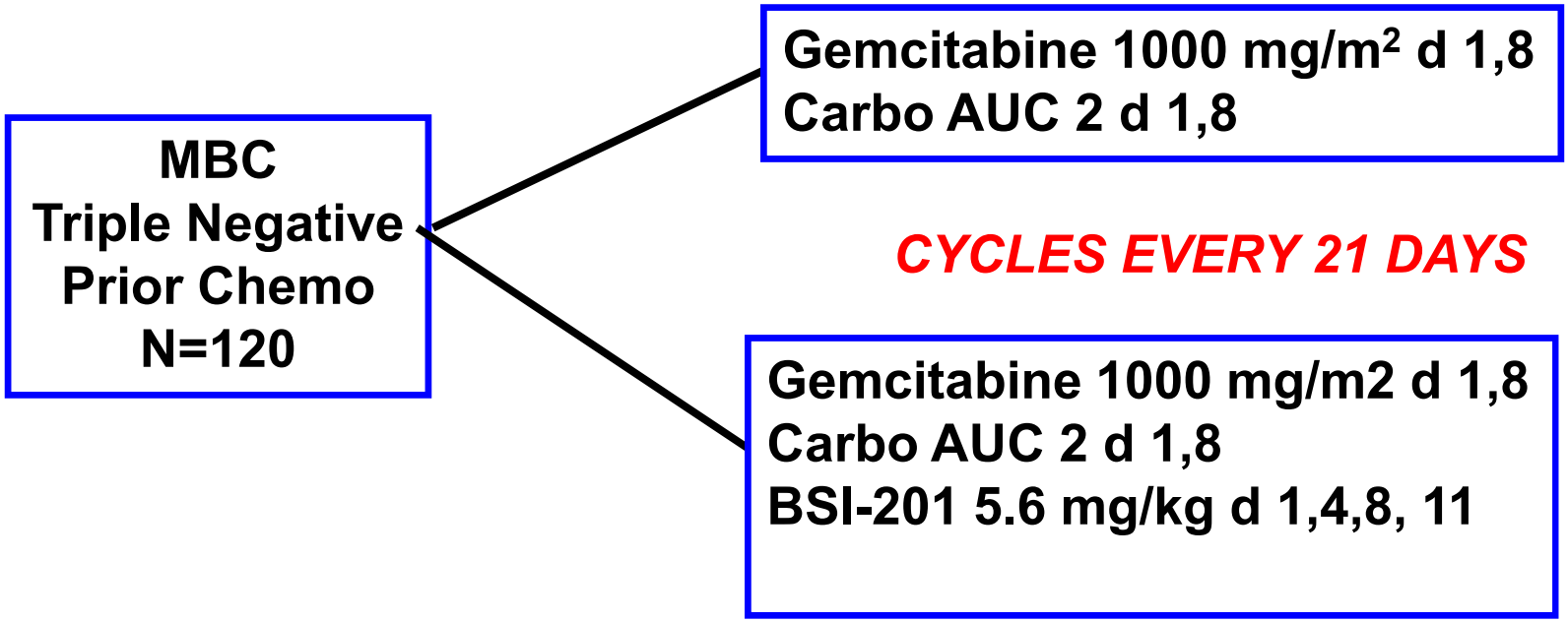
Outside Of A Clinical Trial, the Platinum Salts Are Not Appropriate For Routine Use.

In Your Clinical Practice, Use A Standard Regimen For Adjvuant Or Neoadjuvant Treatment.

PARP Inhibitors Capitalize on Abnormal DNA Damage Repair in BRCA-Associated and Triple Negative Cancers



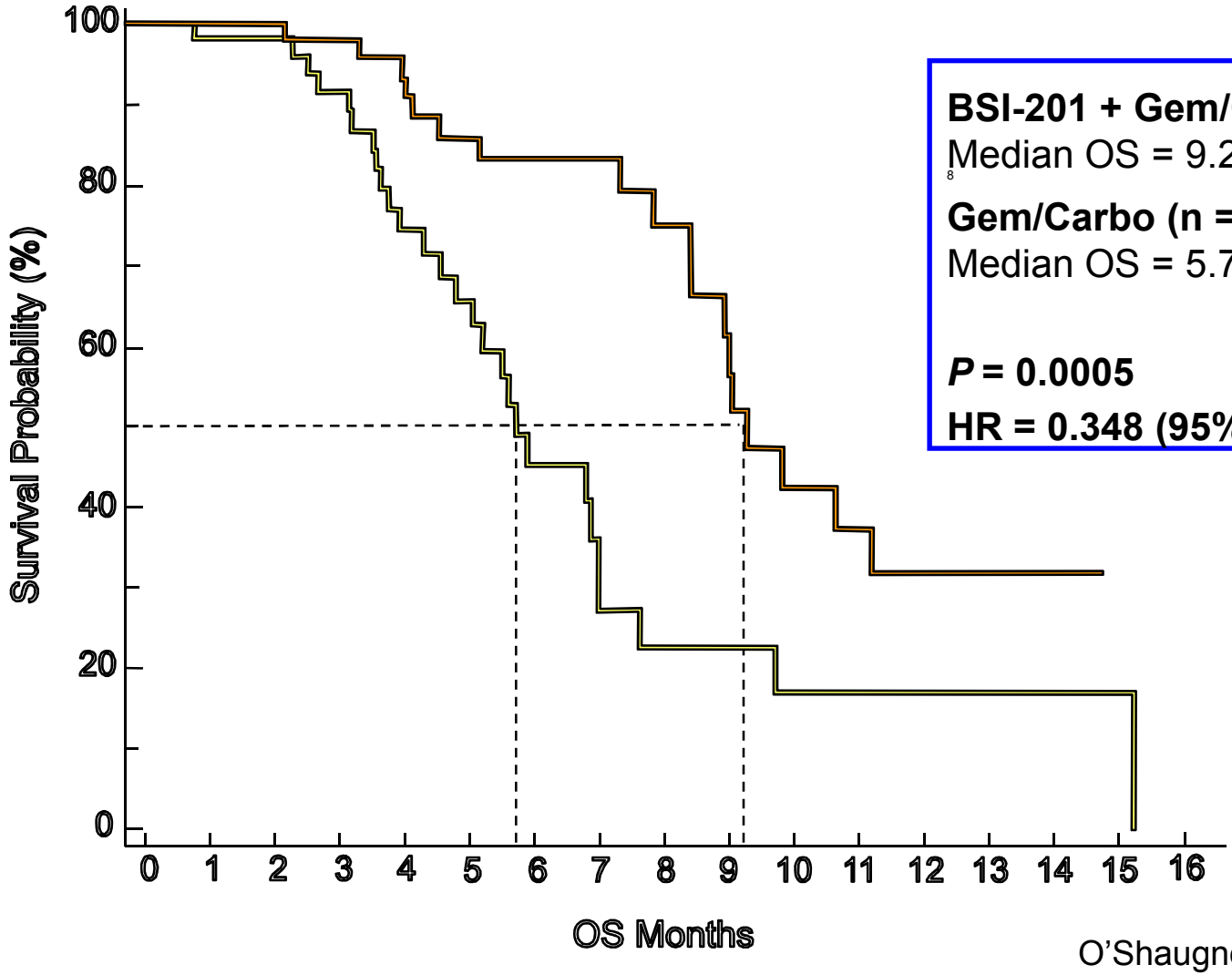
Carboplatin/Gemcitabine +/- BSI-201 in Metastatic Triple Negative Breast Cancer



RESTAGE EVERY 2 CYCLES

O'Shaugnessy et al, ASC0 2009

Carbo/Gem +/- BSI-201: Overall Survival



BSI-201 + Gem/Carbo (n = 57)
Median OS = 9.2 months

Gem/Carbo (n = 59)
Median OS = 5.7 months

***P* = 0.0005**

HR = 0.348 (95% CI, 0.189-0.649)

O'Shaugnessy et al, ASC0 2009

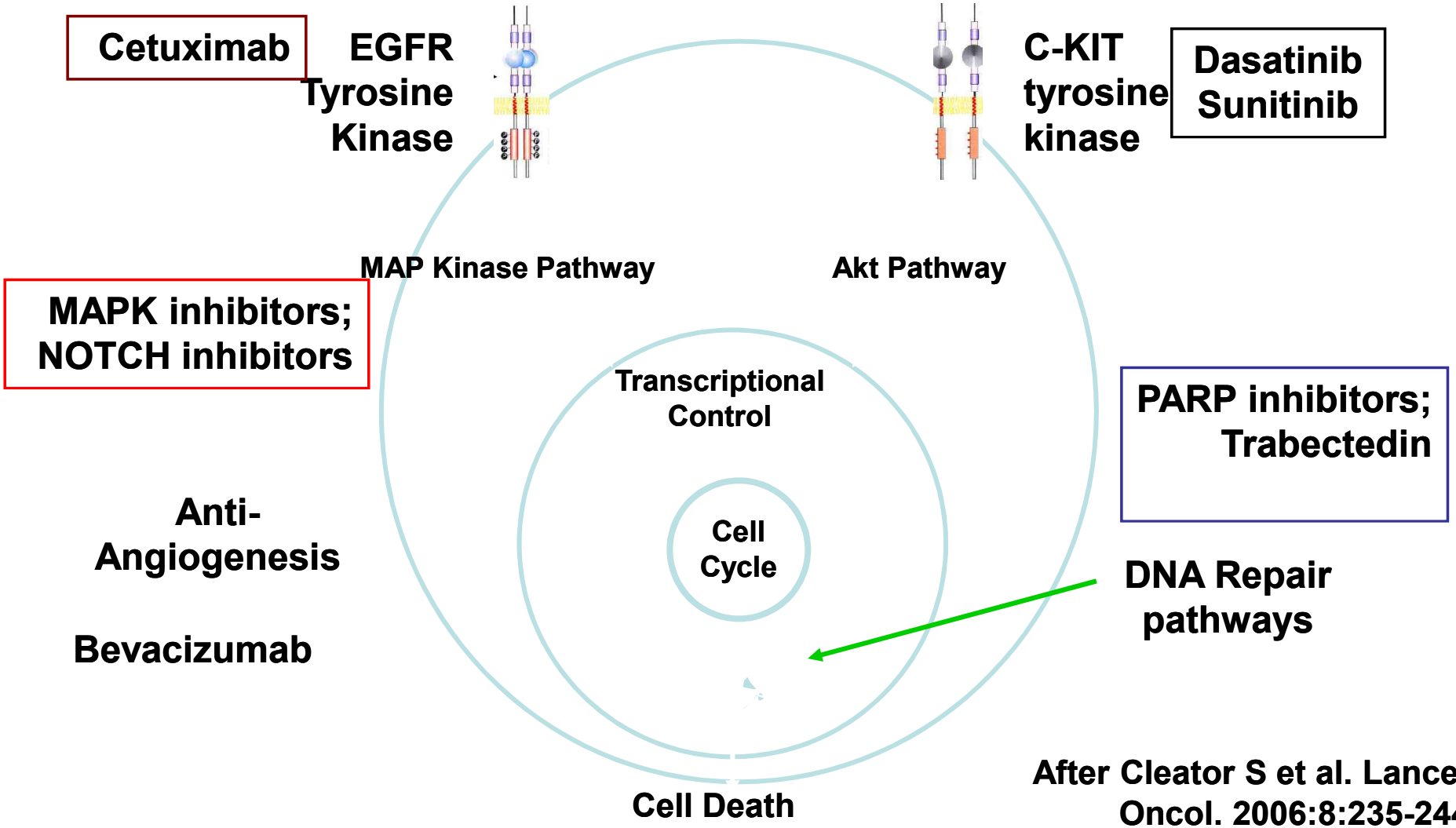
Olaparib BRCA 1 or 2 Mutation Carriers With Metastatic Disease

	Olaparib (n=27) 400 mg bid	Olaparib (n=27) 100 mg bid
Overall Response	41%	22%
Complete Response	4%	0
Partial Response	37%	22%
Median Time To Progression	5.7 months [4.6-7.4]	3.8 months [1.-5.5]

- ***Dose appears to matter wth higher response rate at 400 mg bid***
- ***Prior therapy did not affect response***
- ***Patients with both BRCA1 and BRCA2 responded to treatment***

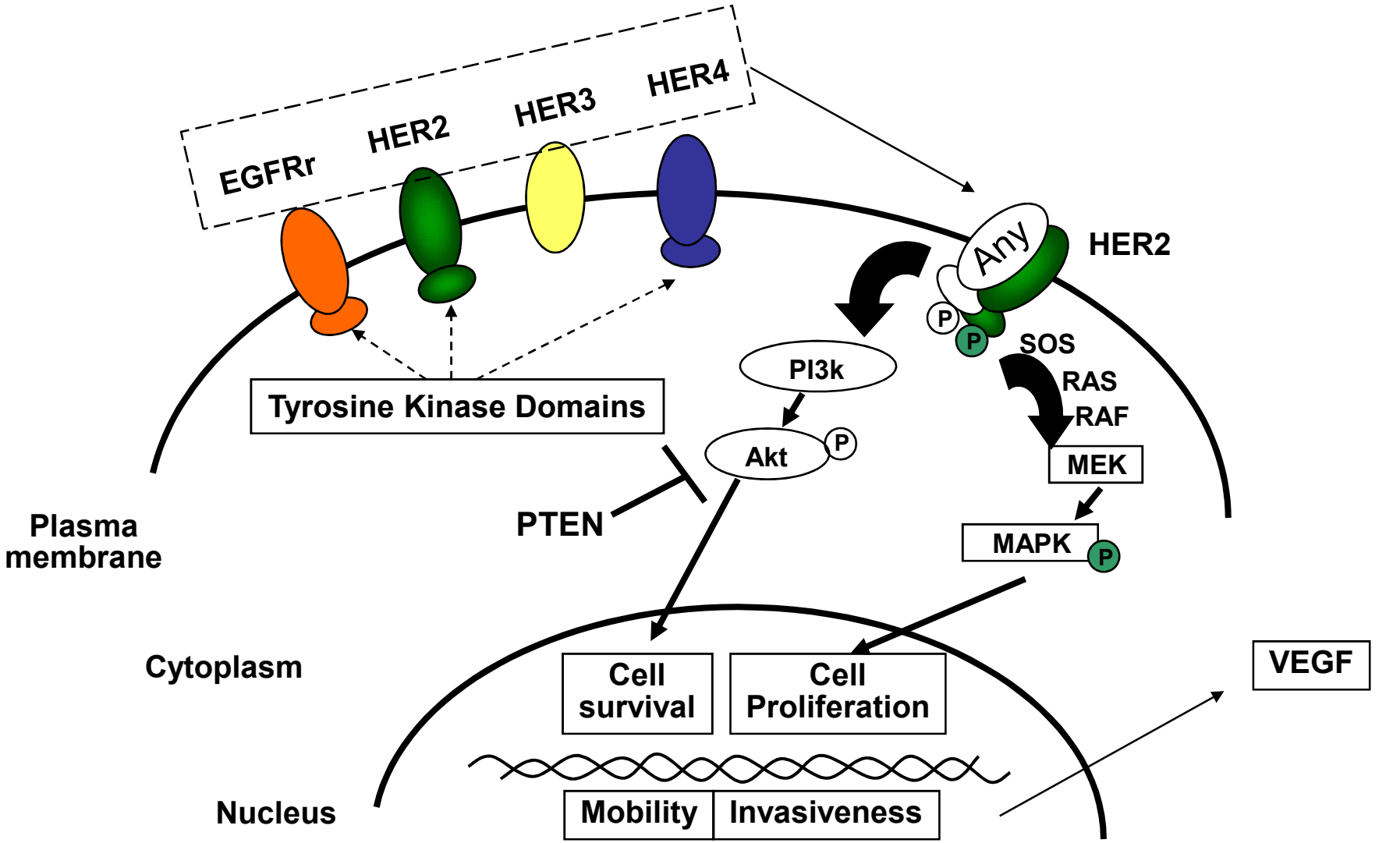
Tutt et al ASCO 2009

Triple-Negative Breast Cancers: Potential Therapeutic Targets



After Cleator S et al. Lancet Oncol. 2006:8:235-244

HER2 Signaling Pathways



Adapted from C. Hudis

Adjuvant HER2+ Trials

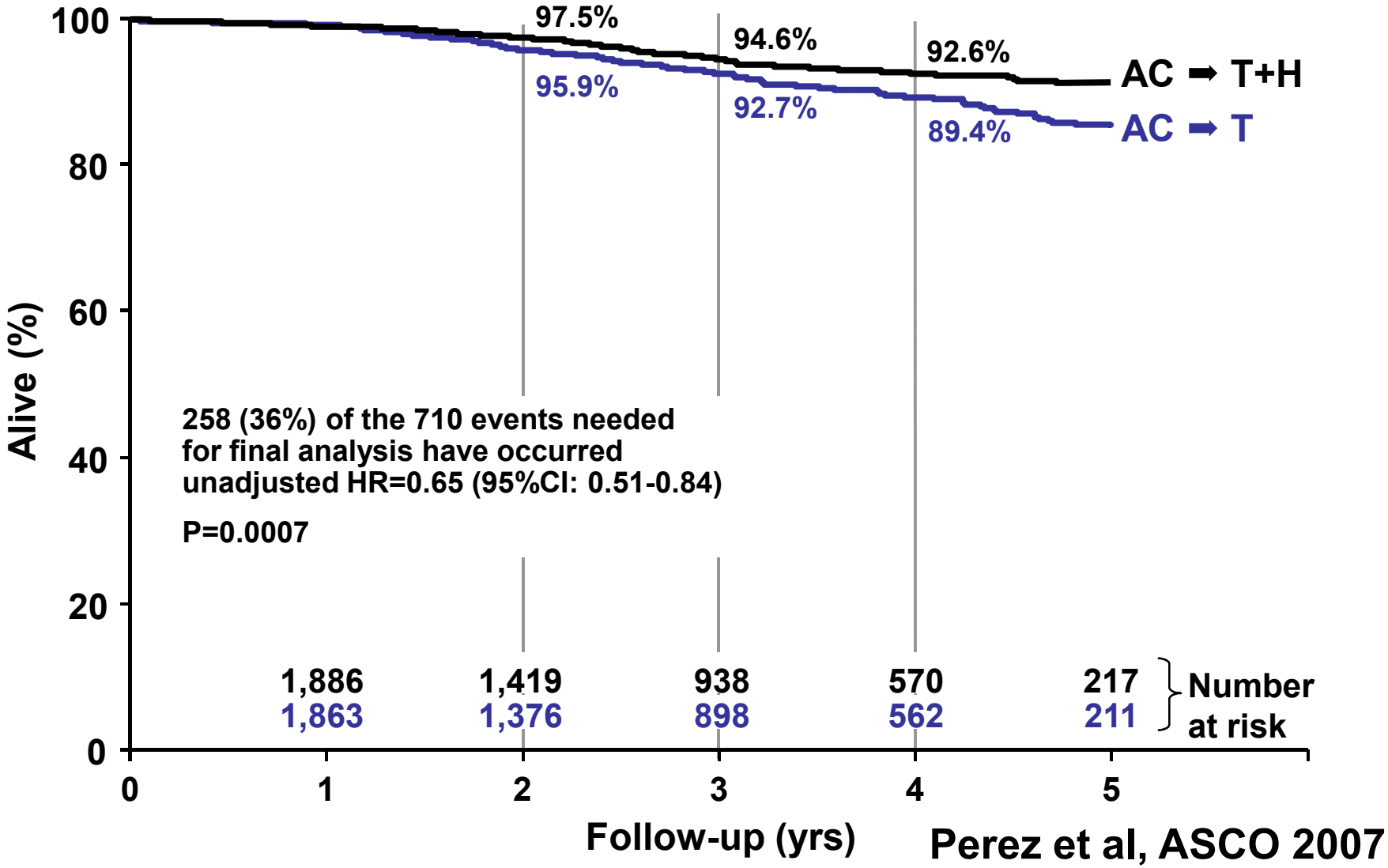
- **NSABP**
- **N 9831 (Intergroup)**
- **HERA**
- **BCIRG**

Large trials each involving 3000+ patients

In total, over 12,000 women entered these trials with over half randomized to receive trastuzumab.

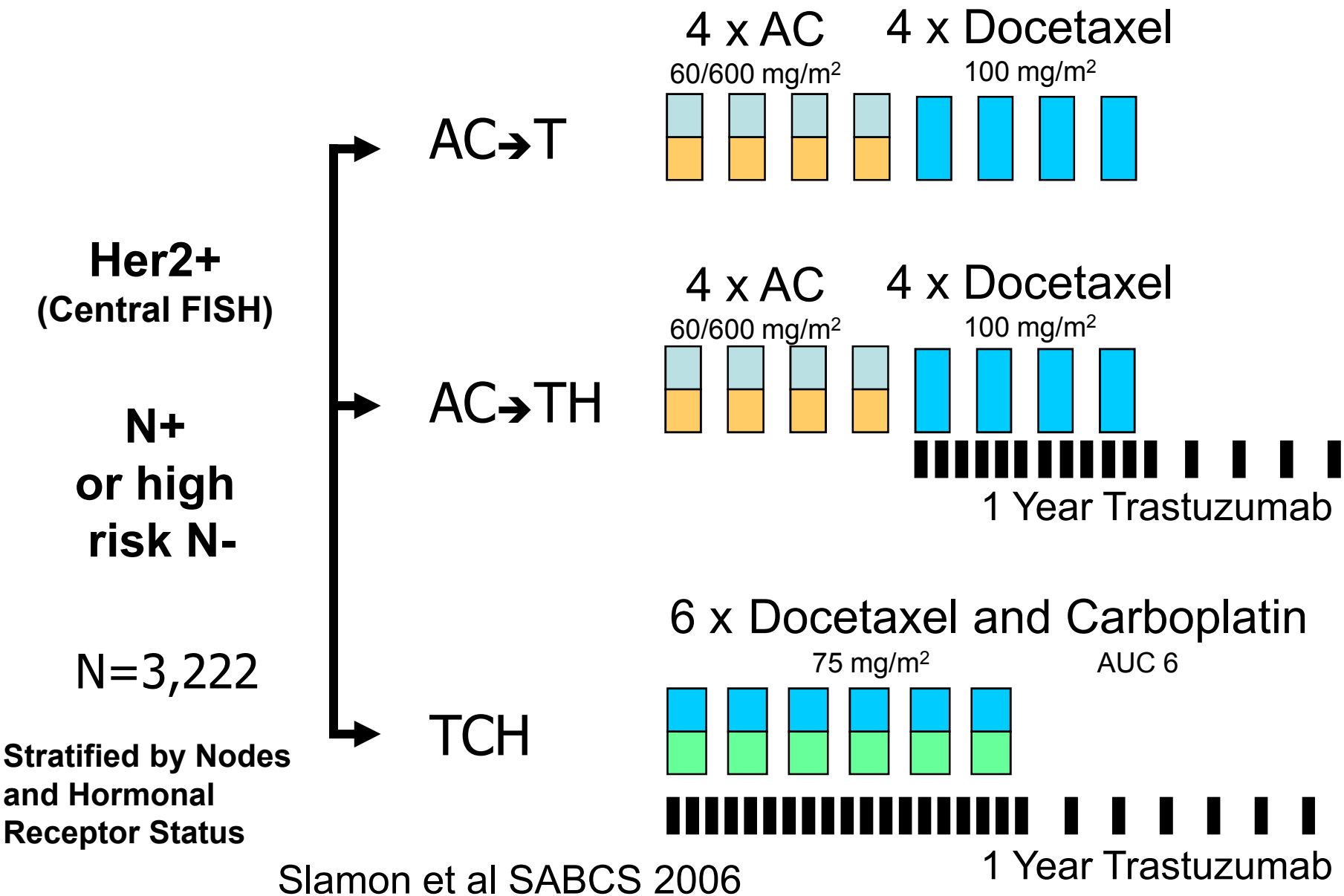
- **FINN HER**

N9831/B-31 Joint Analysis of AC-T +/- Trastuzumab: Overall Survival*



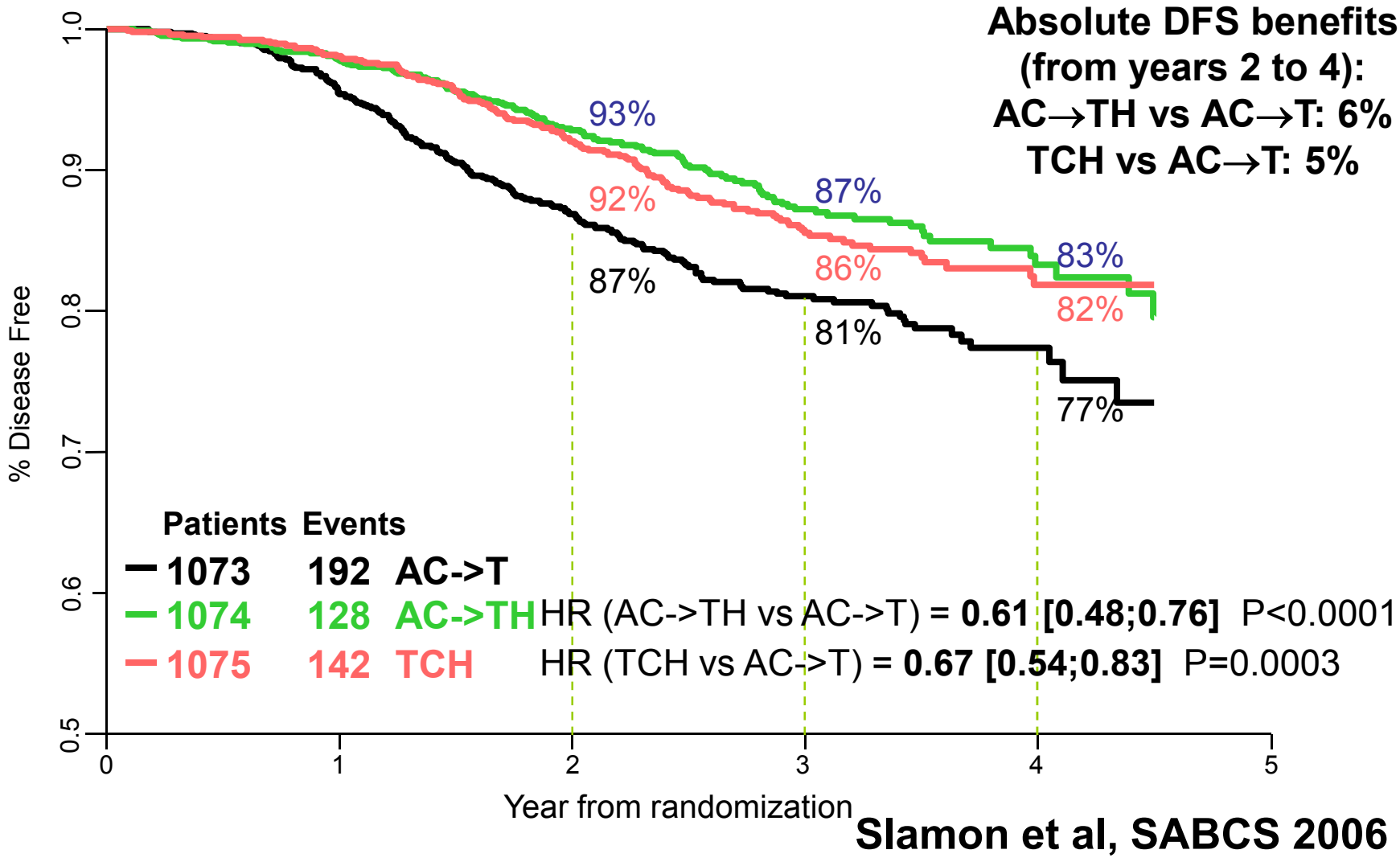
Perez et al, ASCO 2007

BCIRG 006



Slamon et al SABCS 2006

Disease Free Survival: AC-T vs AC-TH vs TCH



Slamon et al, SABCS 2006

Where Are We With HER2+ Disease?

- **With ~85% DFS at 4 years in mostly node positive patients, the questions are:**
  - **Who needs MORE therapy?**
  - **Who needs LESS therapy?**
  - **Who needs DIFFERENT therapy?**
- **My fear is that we will continue to add therapies, much as we did with chemotherapy, without considering who needs LESS!**

Mechanism of Resistance

- **Altered target expression (e.g. change in HER2 status)**
- **Altered target (e.g. mutation in receptor)**
- **Signaling through alternative pathways (e.g. IGFR)**
- **Preferential dimerization with other receptors (e.g. HER3)**
- **Activation of downstream pathway (e.g. PI3k)**
- **Suboptimal drug delivery (e.g. brain metastases)**

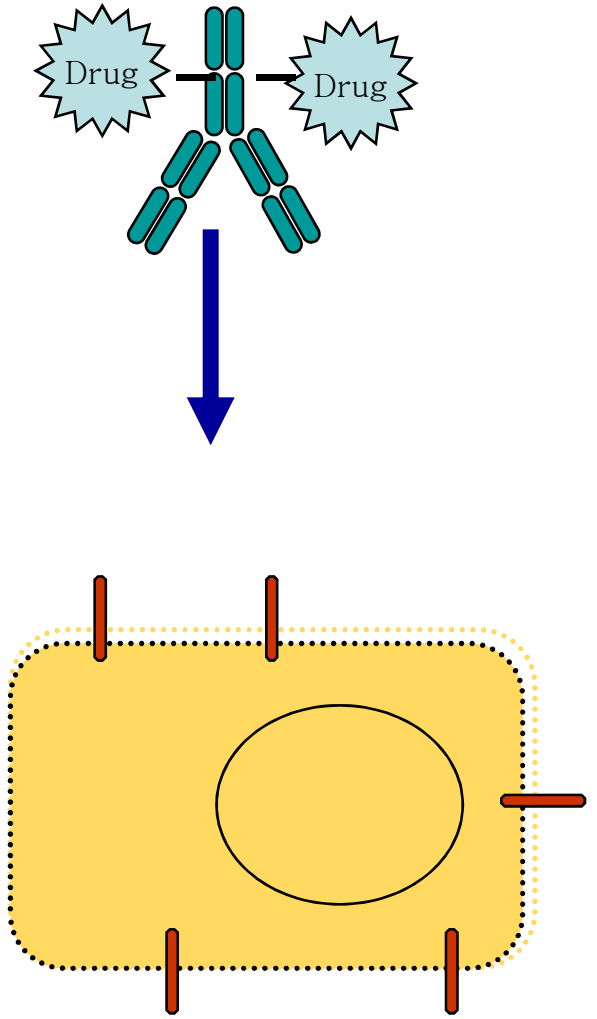
We need to identify and target the resistance mechanisms in individual tumors if we are going to maximize effectiveness and minimize toxicity

New Agents For HER2+ Disease Abound

- Lapatinib
- Pertuzumab (inhibits HER2-HER3 heterodimers)
- HKI (active tyrosine kinase inhibitor of EGFR and HER2)
- Heat shock protein inhibitors
- Angiogenesis inhibitors
- PI3 kinase pathway inhibitors

Trastuzumab-DM1: Novel Antibody Drug Conjugate

- **Delivers high concentrations of drug to tumor**
- **Spares normal tissue from toxicity**



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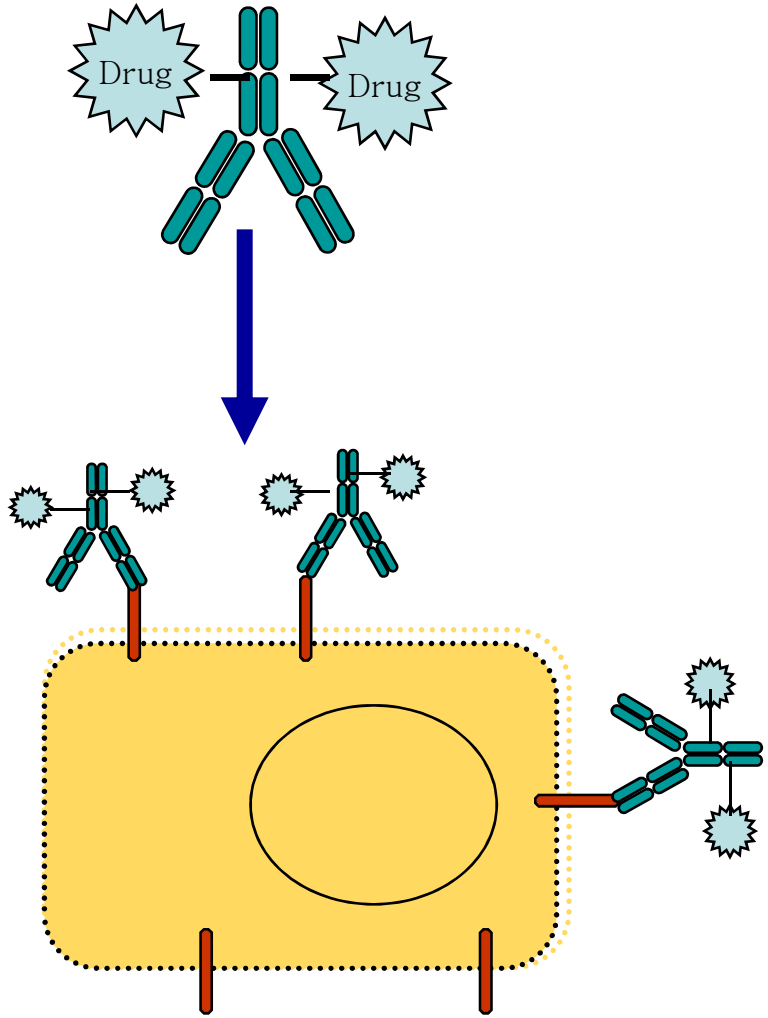

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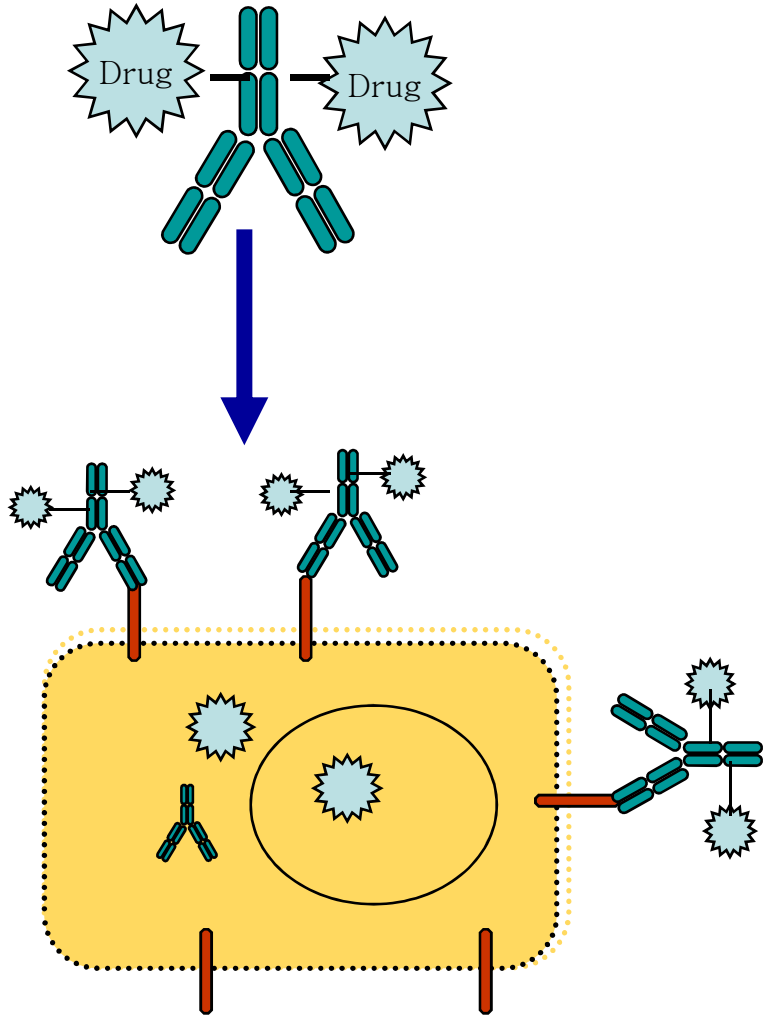

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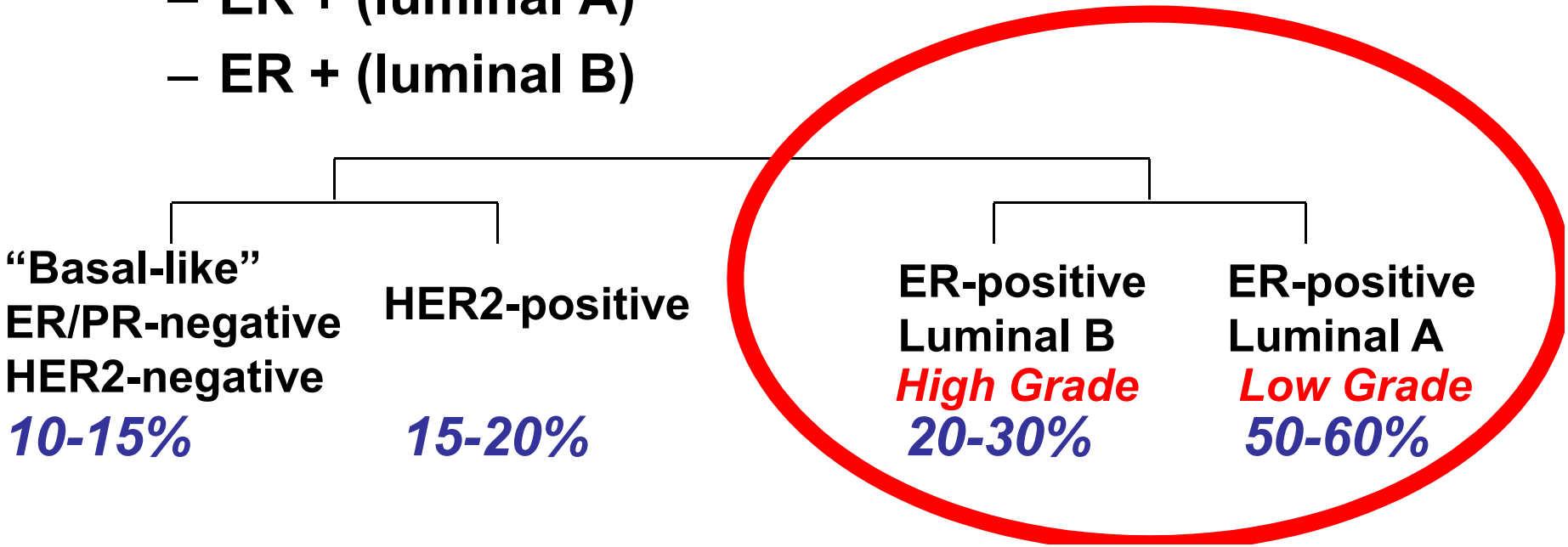


Which Patients With ER+ and HER2 Negative Disease Benefit From Chemotherapy?

70% Of Patients Are In This Subgroup, And Many Have Probably Received Treatment That Did Not Help Them.

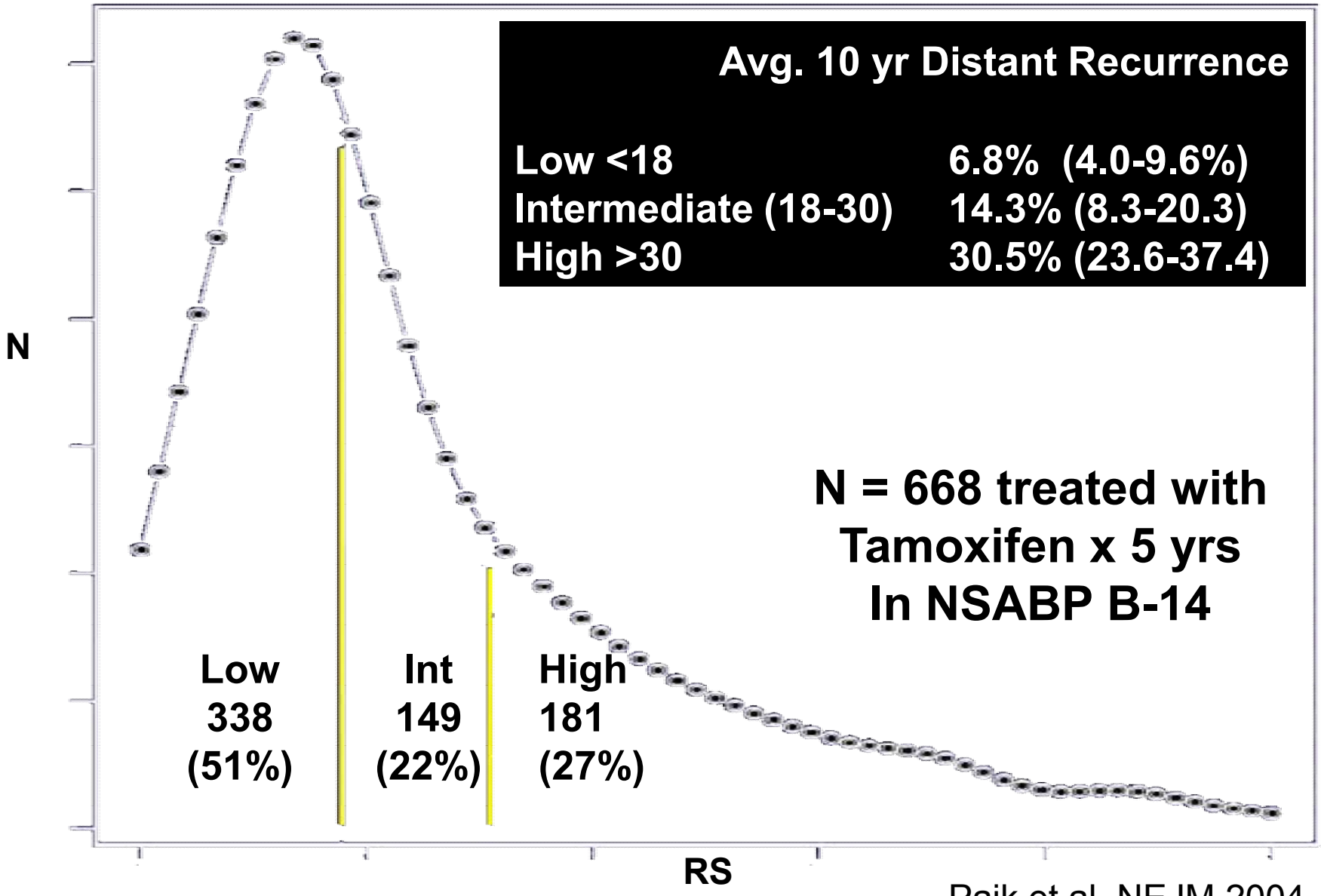
Tumor and Patient Characteristics That Increase Benefit of Chemotherapy in ER+ Disease

- **Level of ER expression**
  - **Best demonstrated with older techniques**
- **Grade**
- **HER2**
- **Measures of proliferation**
- **Genomic predictors**

- **Age**
- **Menopausal status**

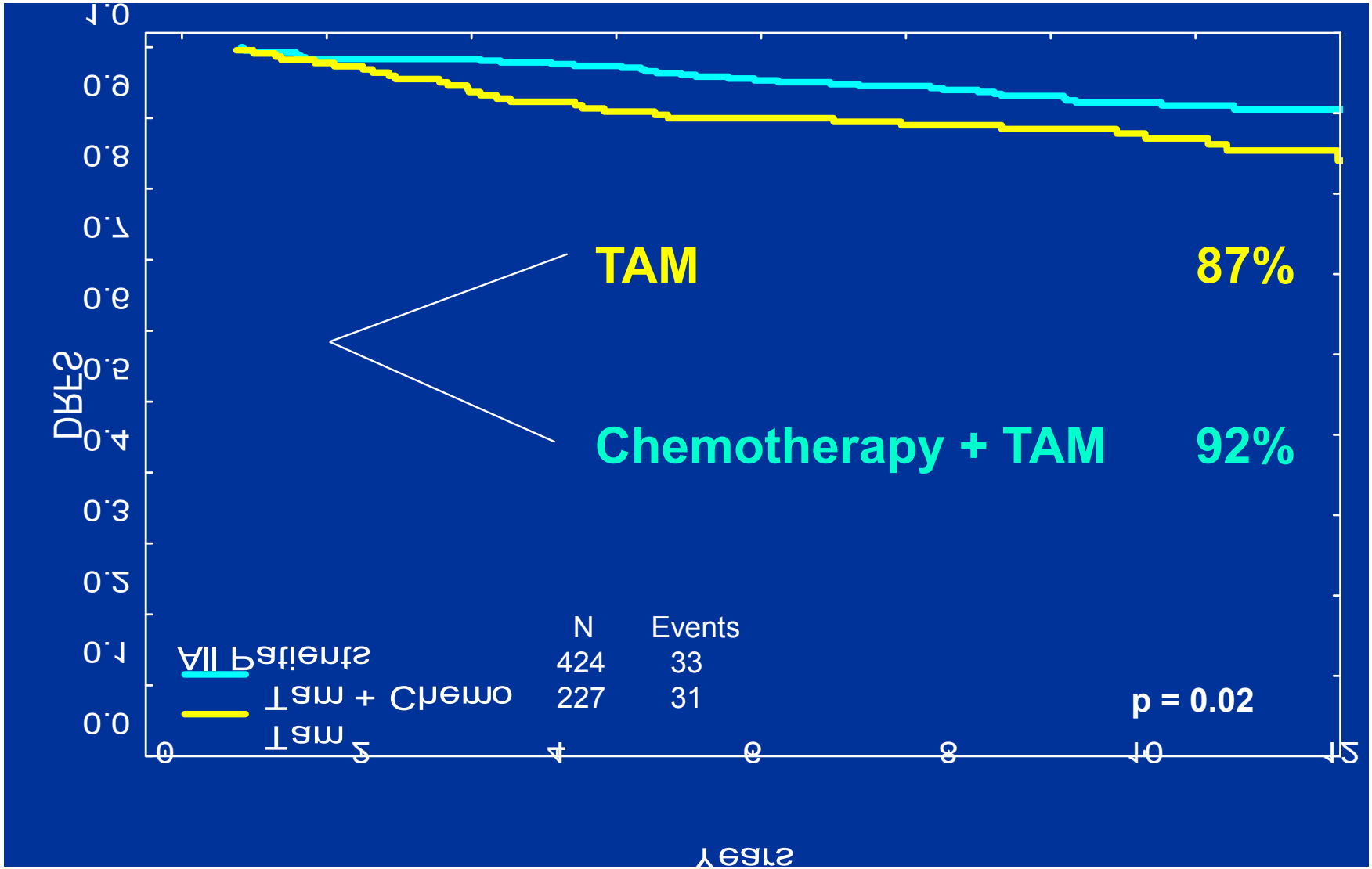
} ***Important if we control for biology?***

Recurrence Score in Node Negative Patients Treated With Tamoxifen For 5 Years



Paik et al, NEJM 2004

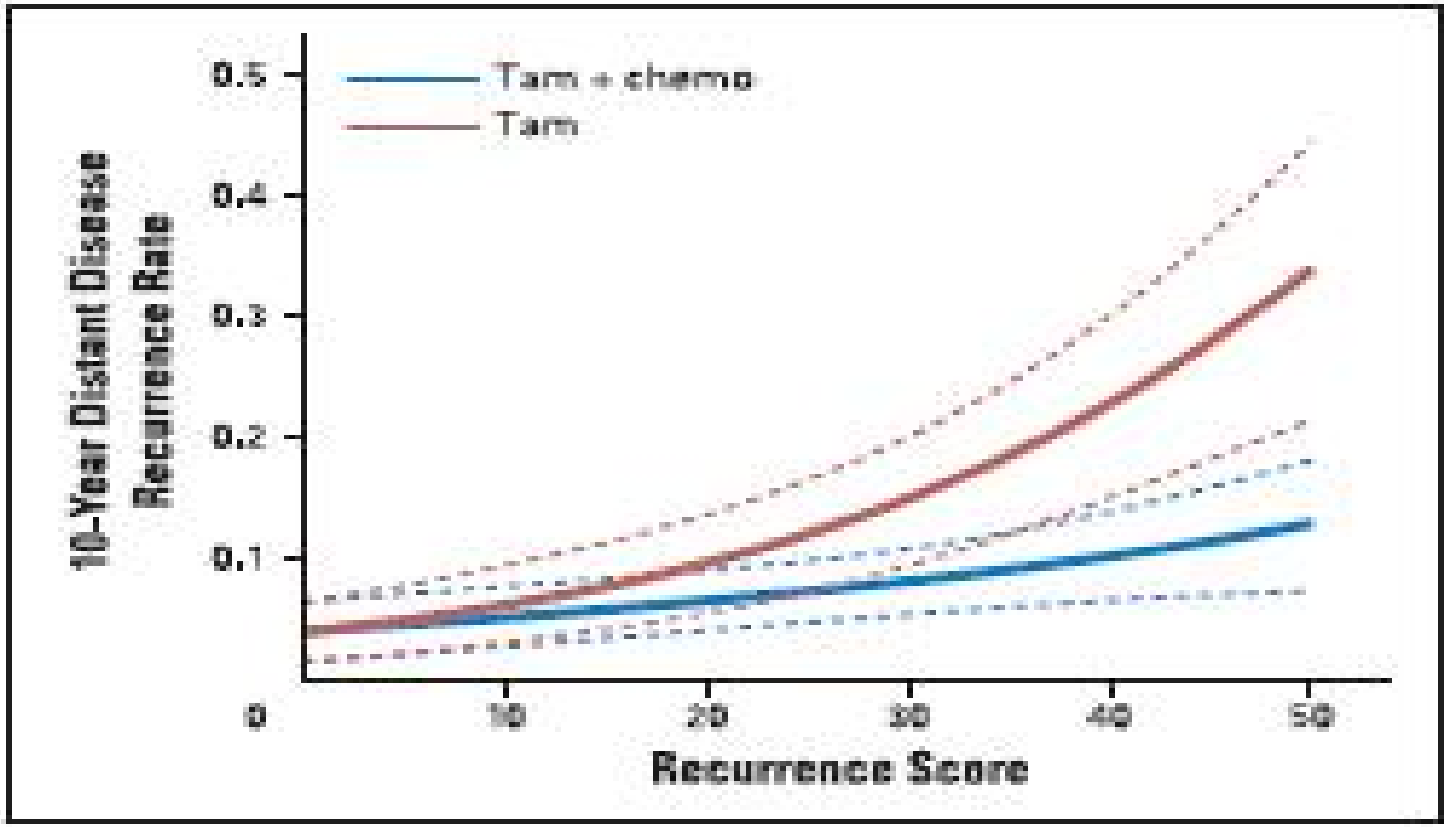
NSABP-20 10 Year Distant Disease-Free Survival



Paik et al JCO 2006: 3726-3724

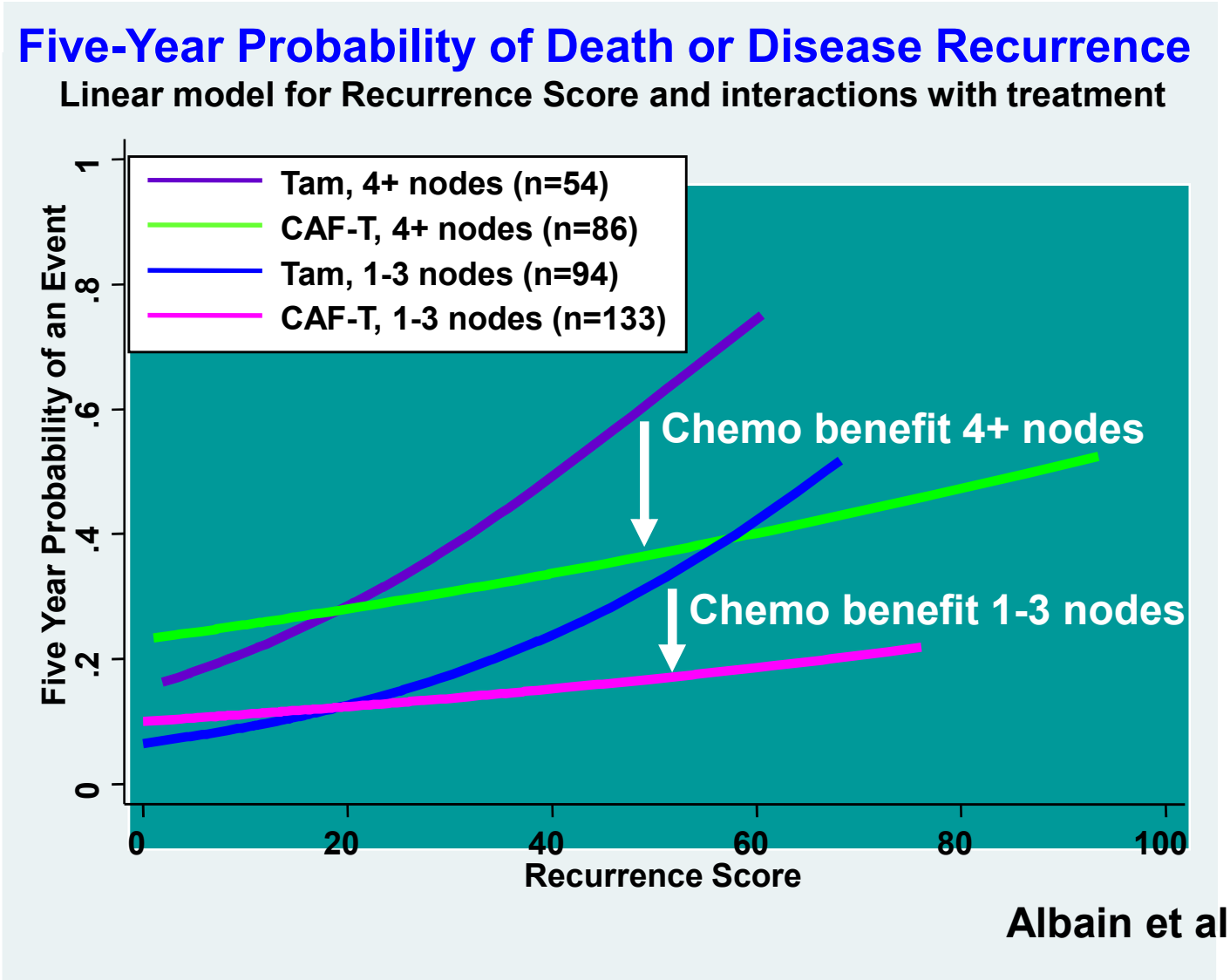
Does Adding Chemotherapy Lower the Risk for These Patients?

It Depends on the Recurrence Score!



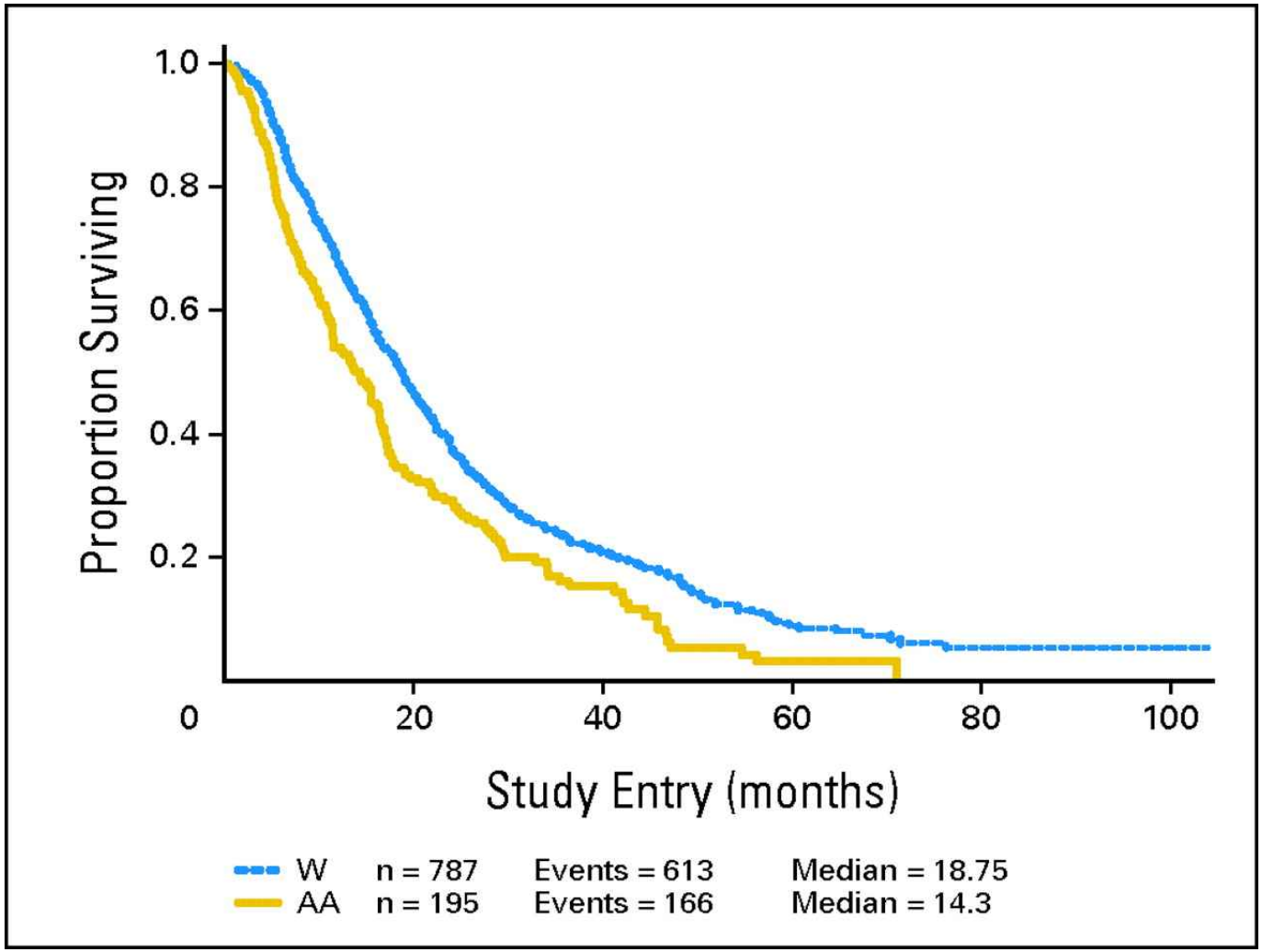
Paik et al, JCO 2006

Similar Findings When CAF Added To Tam In Postmenopausal Women With Node+ Disease



Albain et al, in press

Overall Survival By Race in CALGB Metastatic Paclitaxel Trial (CALGB 9342)



Polite, B. N. et al. J Clin Oncol; 26:2659-2665 2008

So How Do We Move Forward?

Steps 2-5:

- **Respect tumor heterogeneity and intrinsic subtypes**
- **Understand underlying tumor (and host) biology**
- **Collaborate with basic and translational scientists**
- **Be bold – patients with breast cancer want more than a 1% benefit**

Some Challenges…And Some Possible Solutions

- As we subdivide breast cancer, eligible patients will be harder to find

Large, multinational, collaborative efforts must be mounted

- Pharmaceutical companies only want to answer narrow questions and will not take risks

Both academia and foundations must be willing to collaborate with industry

More Challenges….

- The metastatic setting is a more testing ground for new drugs because of the widespread use of adjuvant therapy and the extent of drug resistance

Conduct more neoadjuvant trials

- Tissue is needed for correlative research

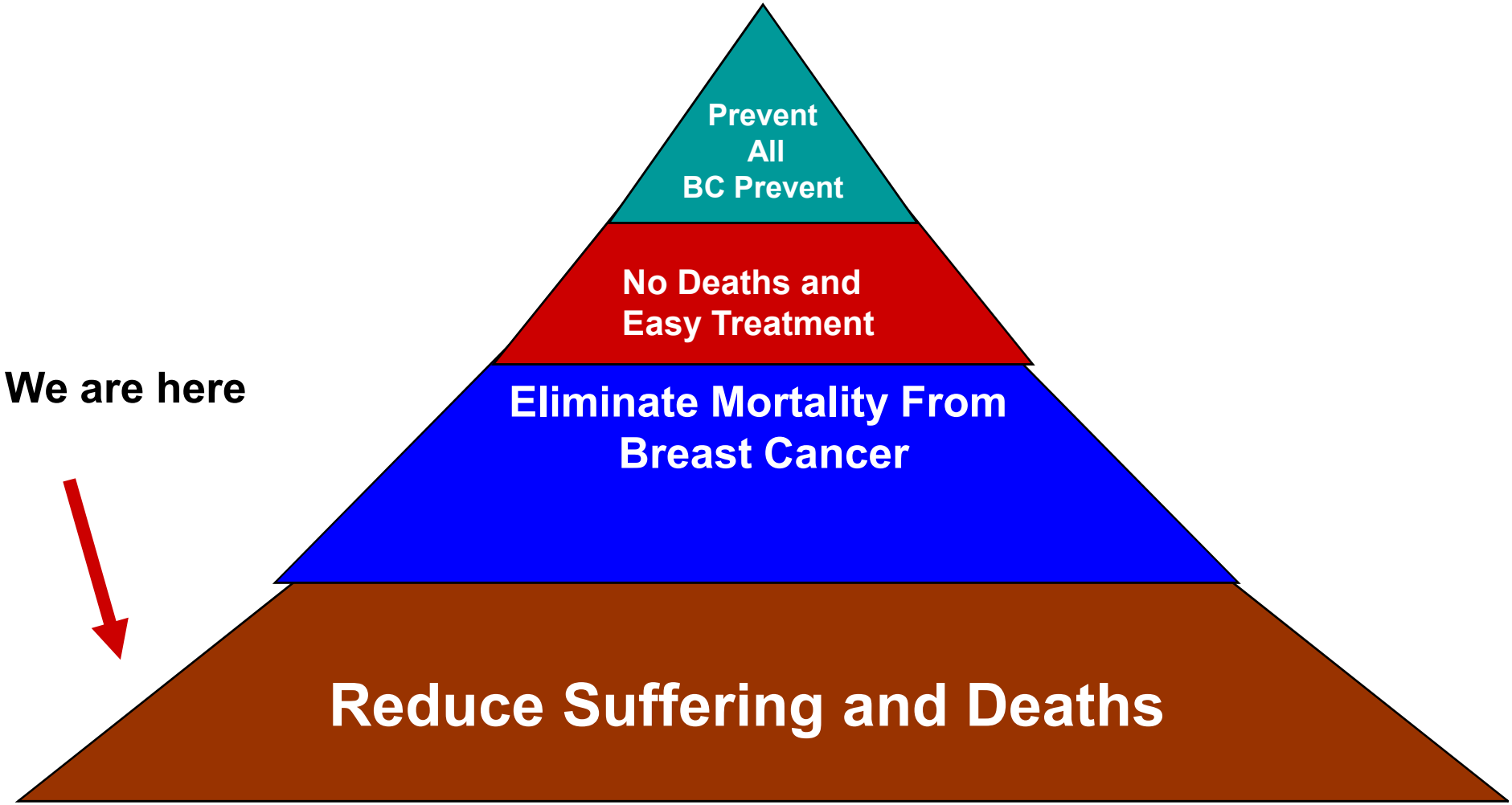
Conduct more neoadjuvant trials

And A Final Challenge….

- Health care disparities both in countries like the U.S. and particularly in other nations limit access to care

Complex issues
Relative success achieved in HIV
Need to consider cost effective strategies
Need to strive to eliminate inequities across all cancer care

Hierarchy of Goals



The Challenge Falls To Us

- **1,000,000 women diagnosed each year**
- **400,000 women lose their lives each year**
- **One woman dies of breast cancer every 1.5 seconds**
- **Laboratory science has blossomed**
- **This is the time to push, to feel a sense of urgency, and to make dramatic strides in the next decade!**