Triple Negative Breast Cancer

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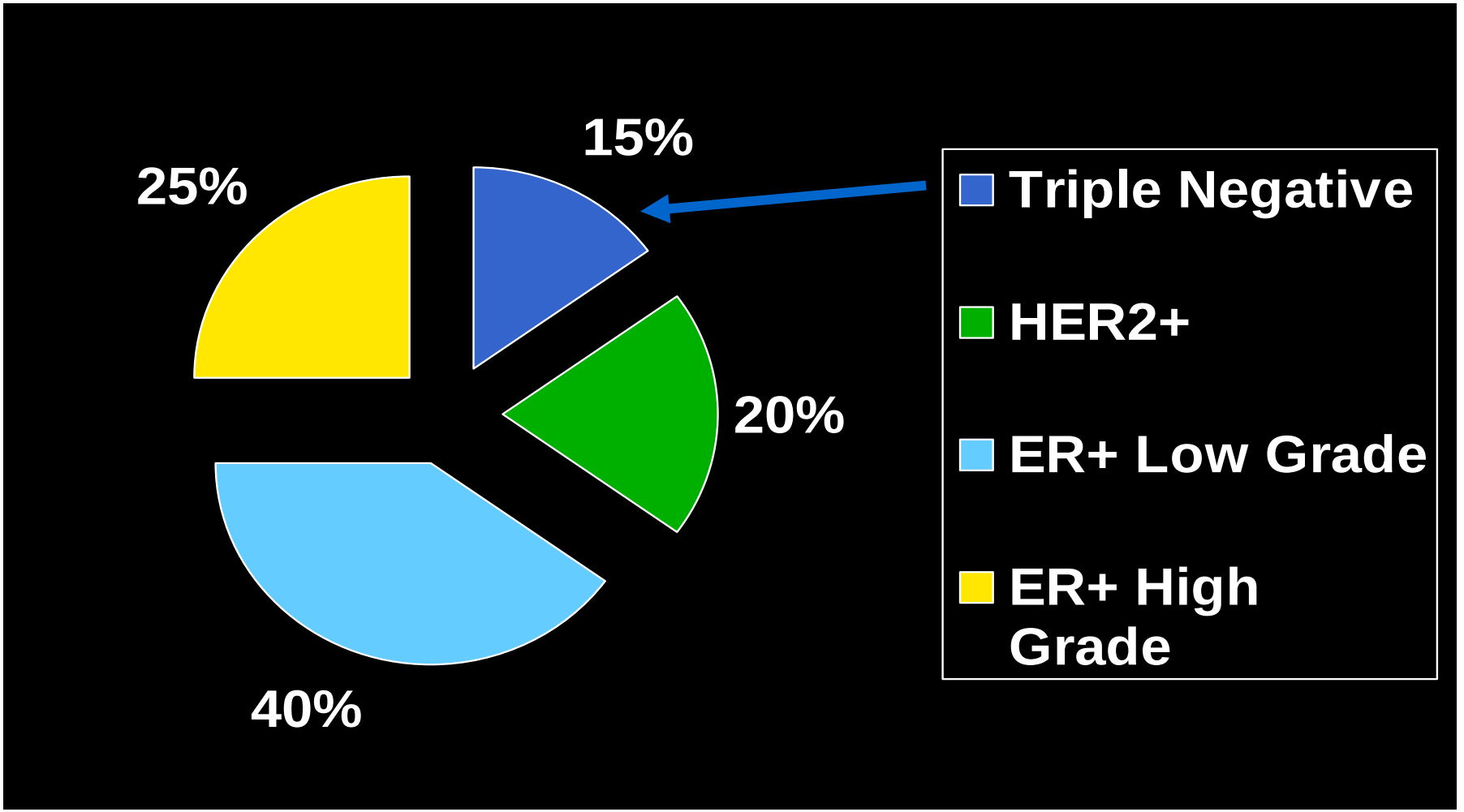
Triple Negative Breast Cancer

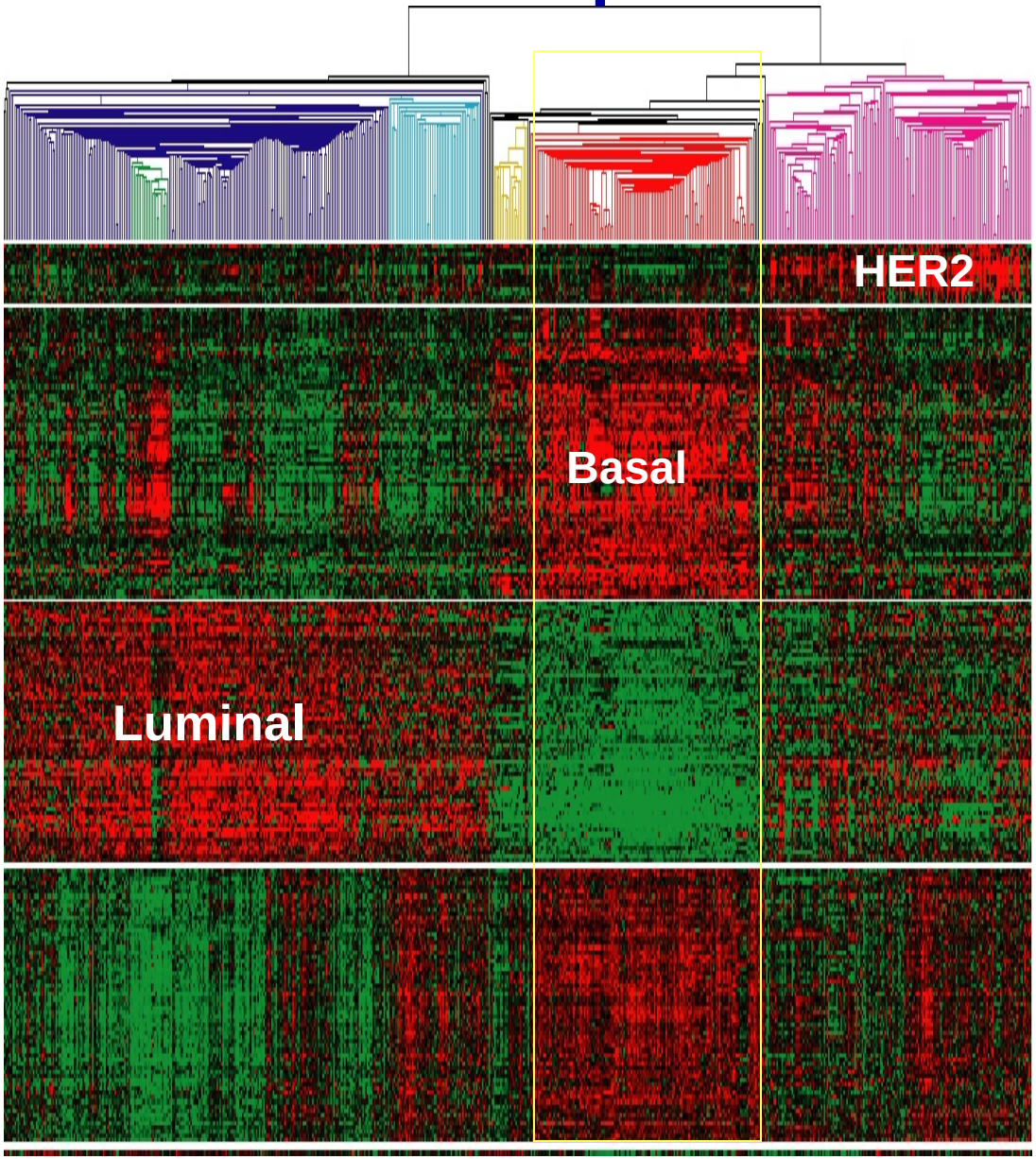


Only approximately 25,000-30,000 cases per year in U.S., but responsible for a disproportionate number of deaths

Triple Negative ≠ Basal-like

- Correlation is high, probably > 80%
- At present, clinical studies will use triple negative as a surrogate for basal-like as arrays are not available for clinical use
- As we search for targets, it is reasonable to explore basal clusters on array studies

Basal-like Breast Cancer: Gene Expression Characteristics



LOW HER2 CLUSTER EXPRESSION

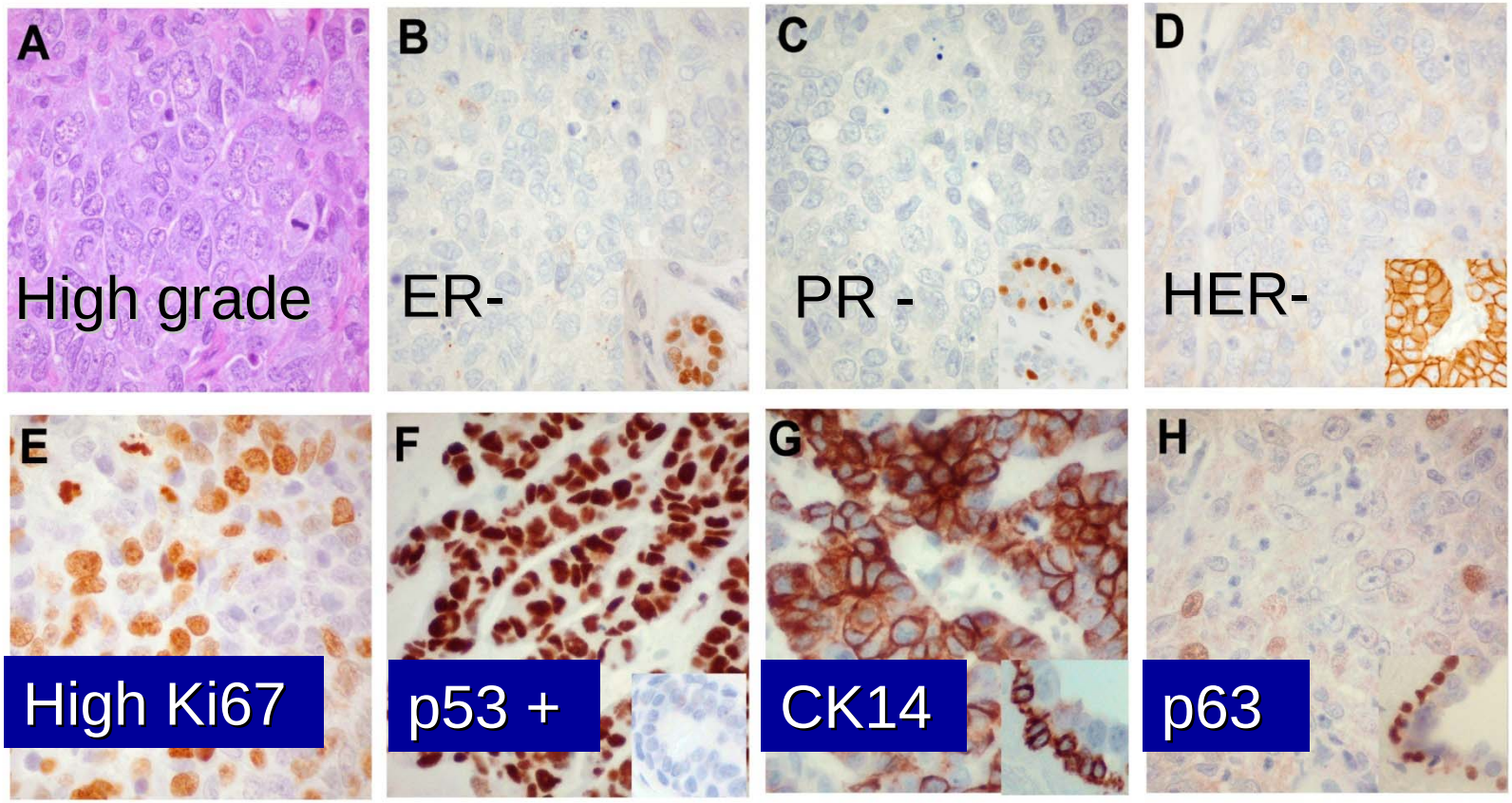
High basal cluster
EGFR
CK 5/6
C-kit

Low ER (and related genes) cluster expression

Highly Proliferative (even more so than HER2 and luminal B)

About 50% p53 mutant

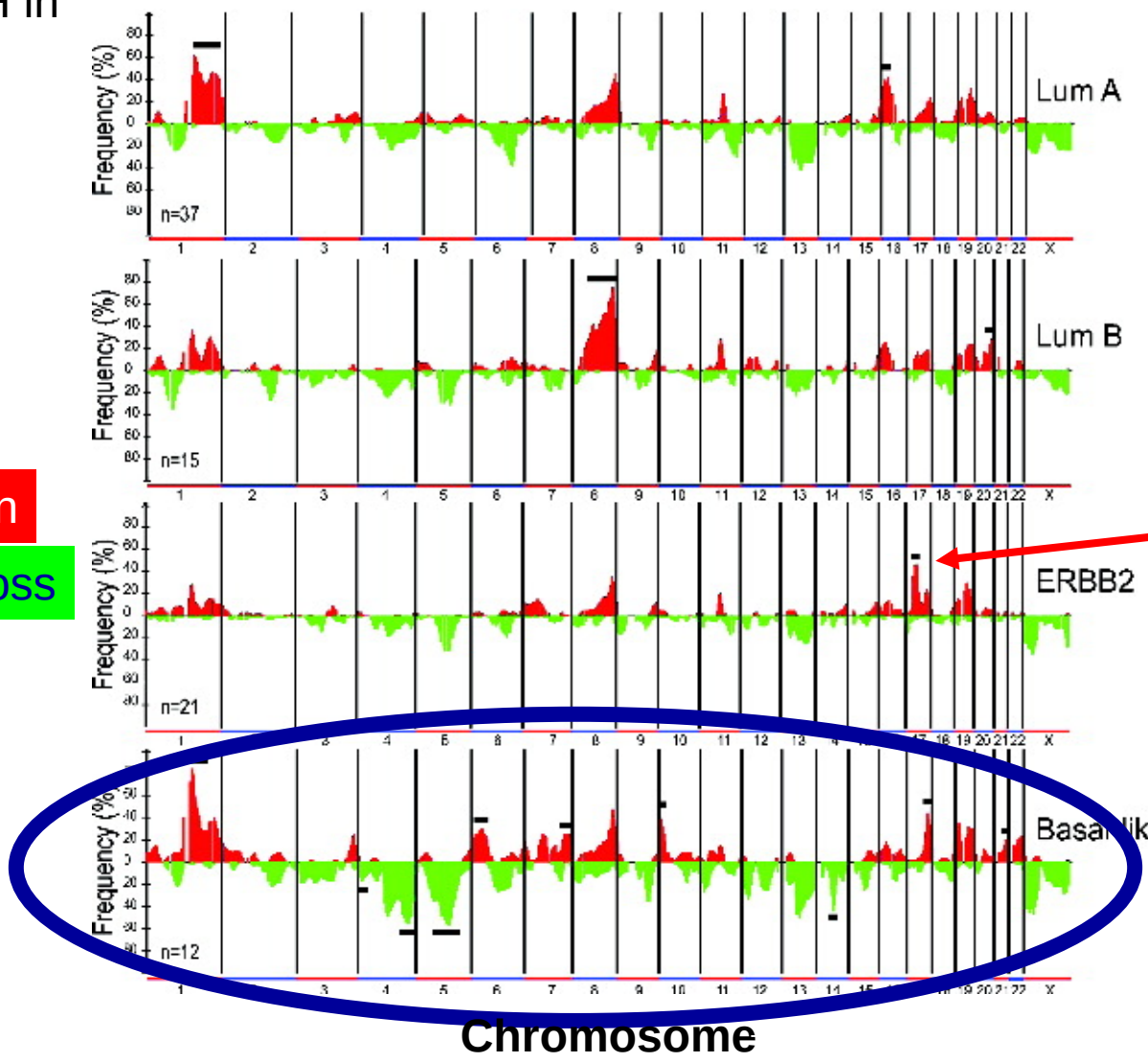
A Prototypical “Basal-like” Tumor



Courtesy of A. Richardson

Basal-like Breast Cancer and Genomic Instability

Array CGH in 89 LABC:



Red=gain

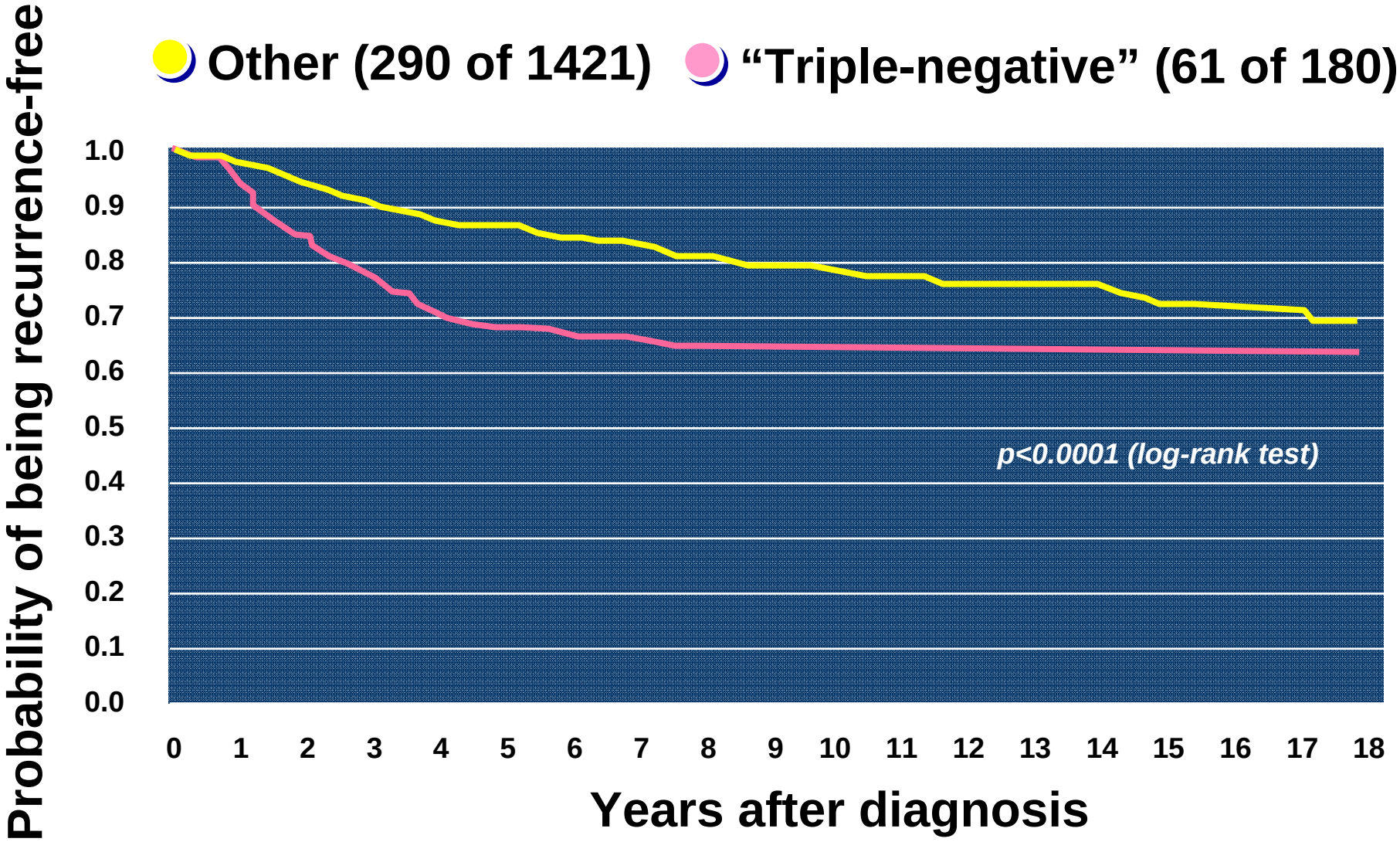
Green=loss

Genome-wide aberrations

Whole and partial chromosome gain and loss

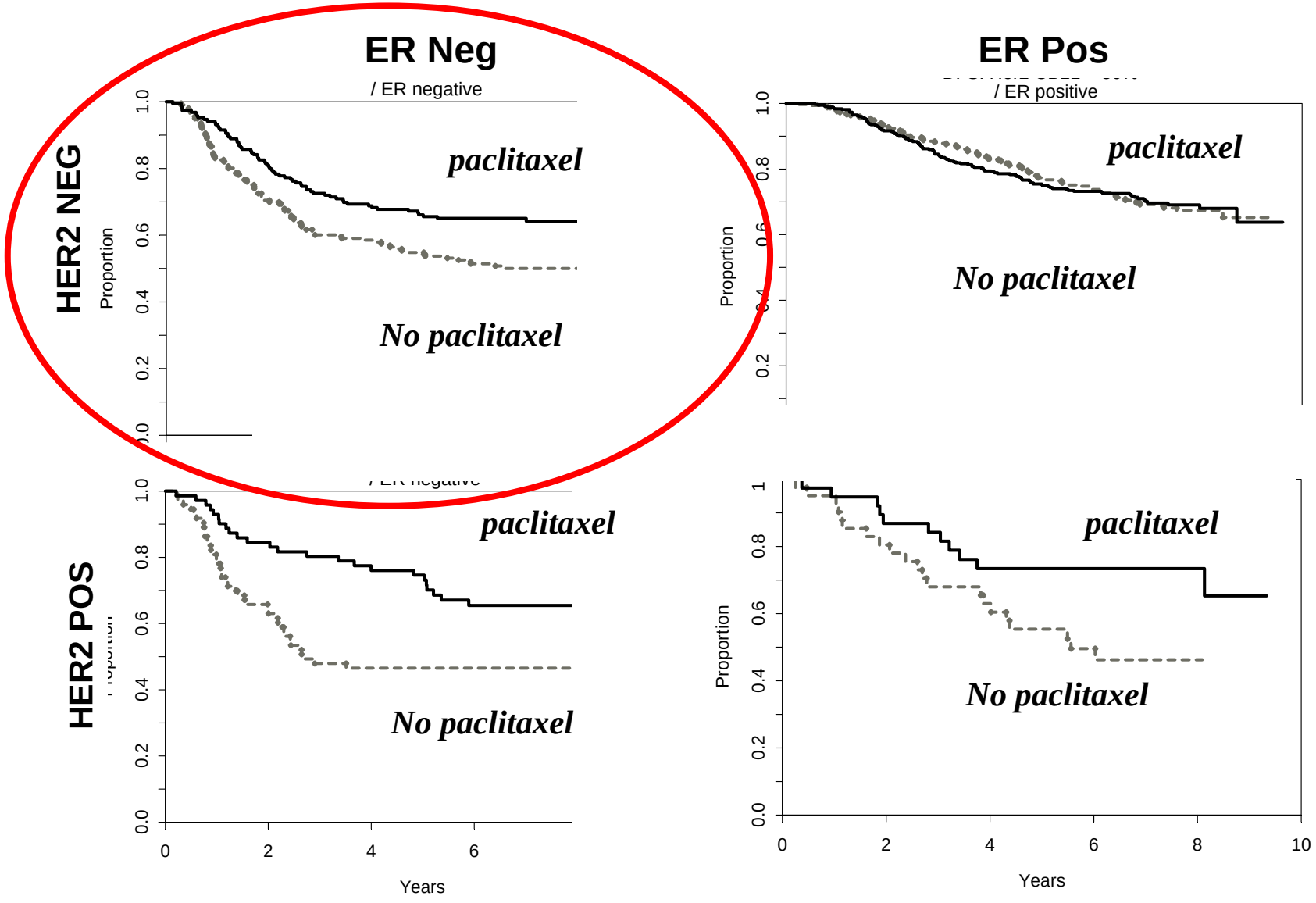
Bergamaschi, Genes Chromosomes Cancer '06

Henrietta Banting Breast Center
Distant Recurrence – F/U 8.1 years



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

CALGB 9344 Disease-free Survival by ER and HER2

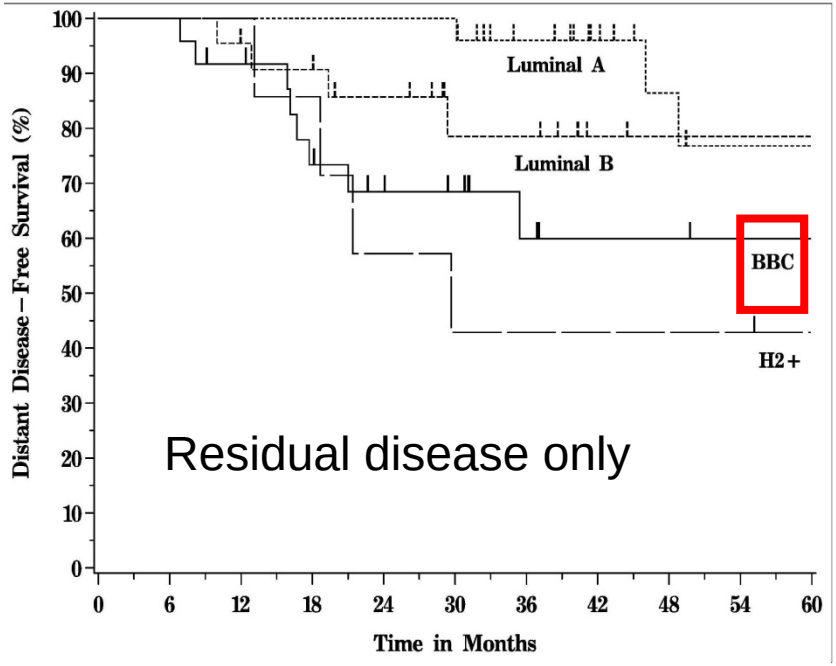


Hayes et al. NEJM 2007

Basal-like Breast Cancer:Pathologic Response to Neoadjuvant Anthracycline/Taxane

Pathologic CR Rate

	T-FAC (N=82)*	AC-T (n=107)*
Luminal A/B	**7%**	**7%**
Normal-like	**0**	**NA**
HER2+/ER-	**45%**	**36%**
Basal-like	**45%**	**26%**

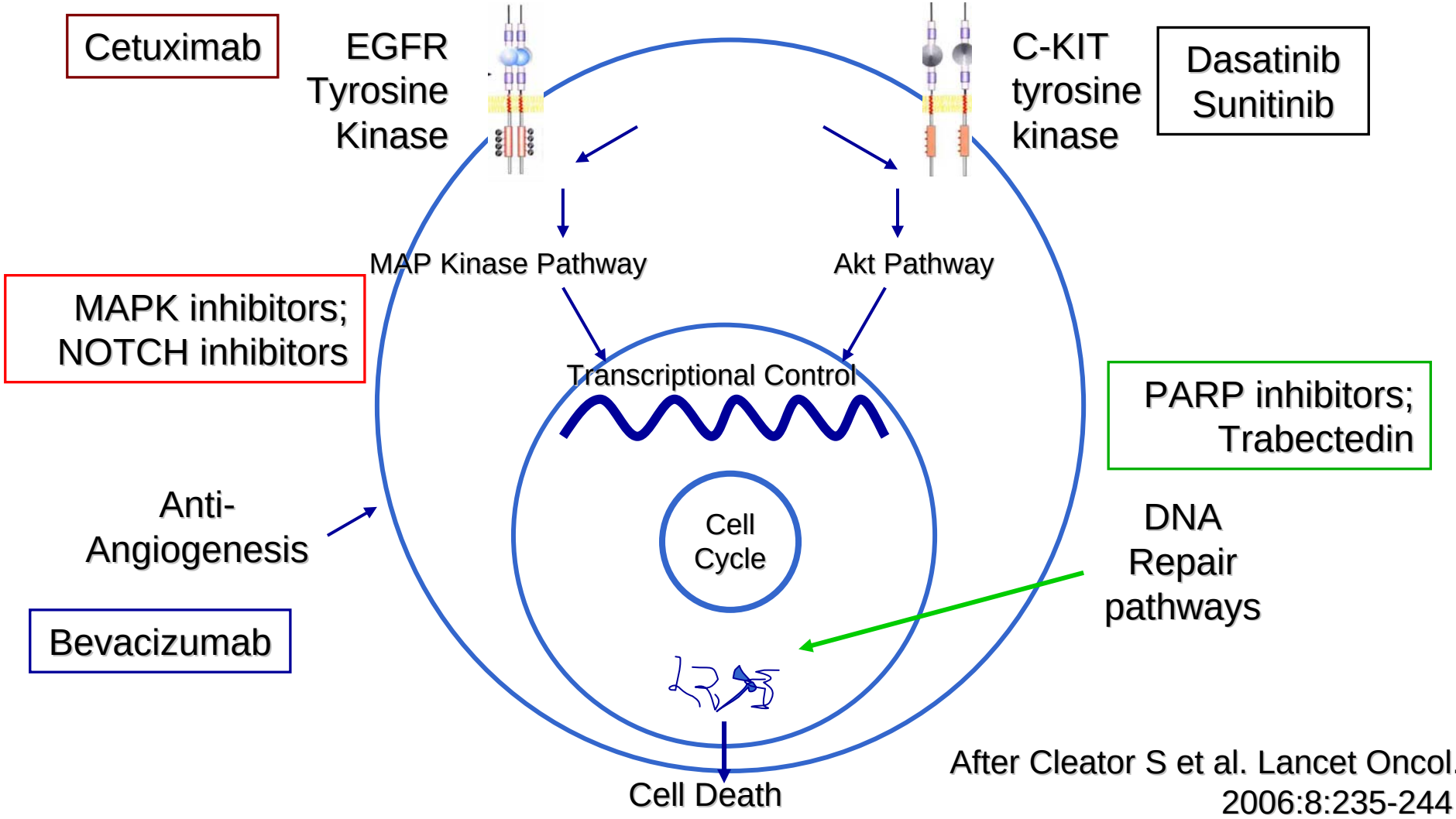


- Good outcome in pCR (>90% 5y DDFS)

- Residual disease in pts with triple negative disease associated with poor prognosis
- Additional therapy needed – what?

Rouzier, Clin Cancer Res' 05; Carey, Clin Cancer Res'07

Triple-Negative Breast Cancers: Potential Therapeutic Targets

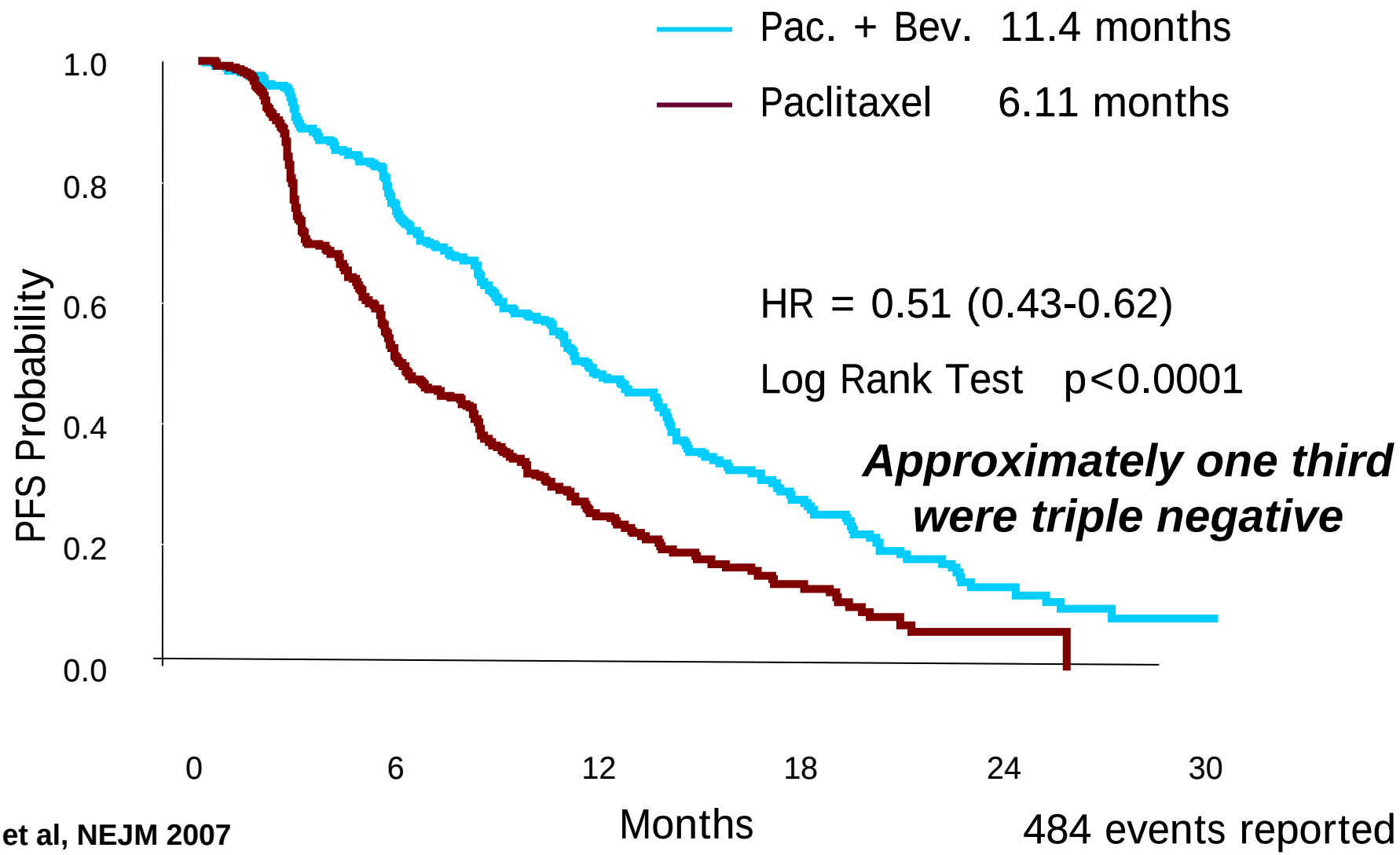


After Cleator S et al. Lancet Oncol. 2006:8:235-244

New Therapeutic Approaches

- **Angiogenesis inhibitors**
- **Tyrosine kinase inhibitors**
- **Platinum-based chemotherapy**
- **PARP inhibition**

Progression Free Survival
Paclitaxel vs Paclitaxel + Bevacizumab

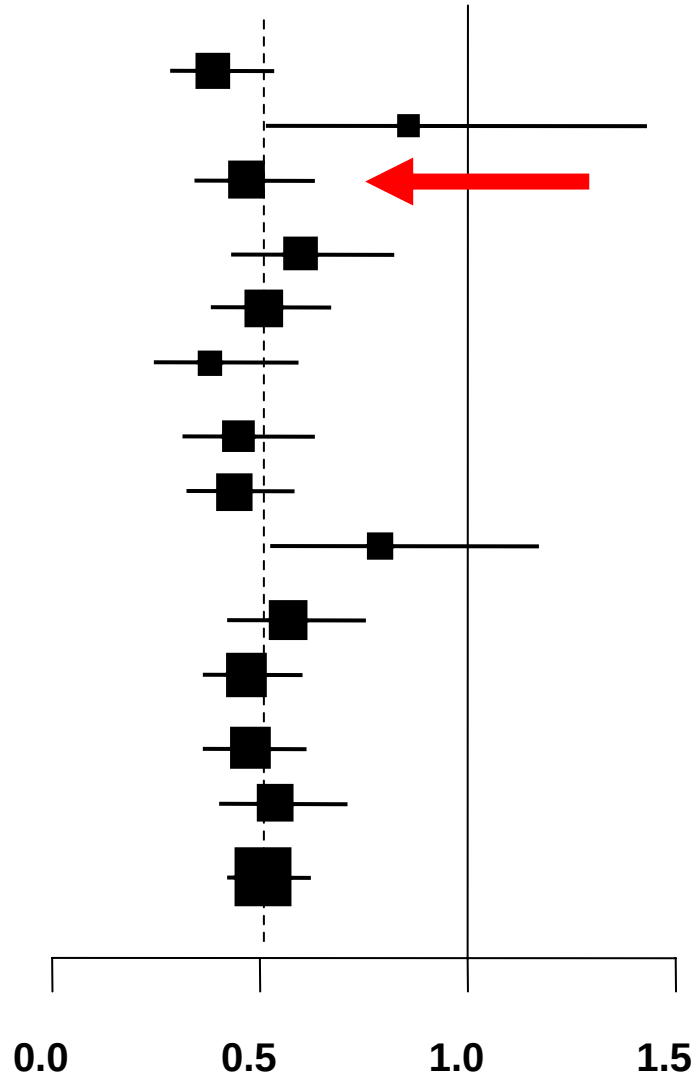


Miller et al, NEJM 2007

484 events reported

Bevacizumab in Clinical Subsets

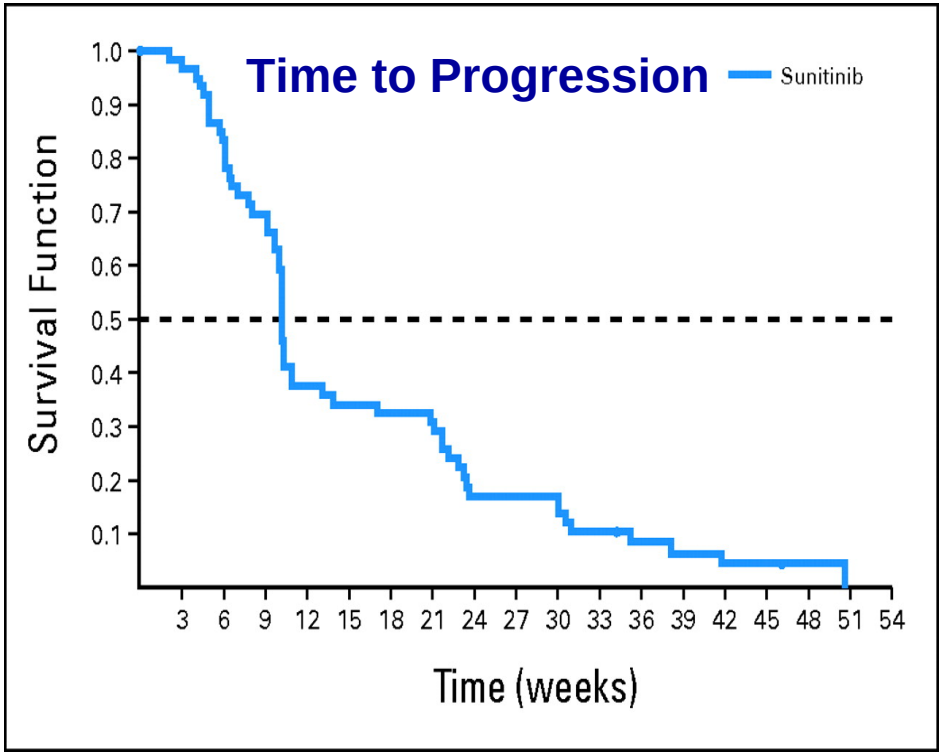
Group	Ratio	95% Conf Int	N
ER+, PR+	0.39	(0.29, 0.53)	200
ER+, PR-	0.86	(0.52, 1.43)	80
ER-, PR-	0.47	(0.35, 0.63)	184
No adj chemo	0.60	(0.44, 0.82)	178
Non-taxane	0.51	(0.39, 0.67)	234
Taxane	0.38	(0.25, 0.59)	86
Age 27 - 49	0.45	(0.32, 0.63)	155
Age 50 - 64	0.44	(0.33, 0.58)	232
Age 65 - 85	0.79	(0.53, 1.17)	111
DFI 0 - 24 mos.	0.57	(0.43, 0.75)	204
DFI > 24 mos.	0.47	(0.37, 0.60)	294
< 3 sites	0.48	(0.37, 0.61)	252
3 or more sites	0.54	(0.41, 0.71)	245
Overall	0.51	(0.43, 0.62)	680



Miller K, NEJM 2007

Phase II Trial of Sunitinib in Patients with Refractory Breast Cancer

- N=64
- ORR 7/64 = 11%
- ORR 3/20 = 15% in triple negative



- ?? VEGF-R inhibition vs c-kit inhibition vs both vs neither

Burstein et al, JCO 2008

EGFR Inhibitors in Breast Cancer

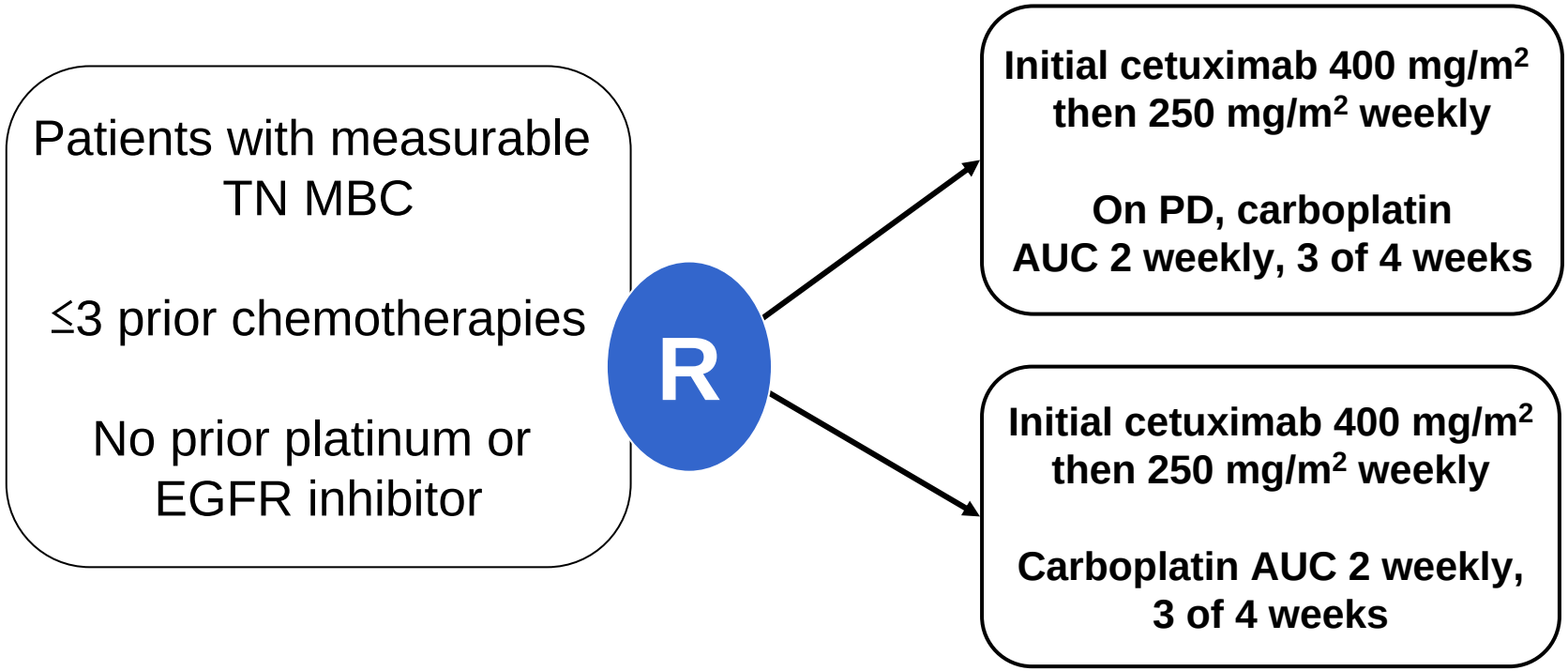
In unselected metastatic breast cancer, single agent EGFR inhibitors have not shown great activity:

• **Phase II ZD1839 (Robertson)**	**2/27 PR**	**6/27 SD**
• **Phase II ZD1839 (Baselga)**	**0/31 PR**	**12/31 SD**
• **Phase II OSI-774 (Winer/Dickler)**	**1/69 PR**	**3/69 SD**
• **Phase II ZD1839 (Albain)**	**1/63 PR**	**7/63 SD**

Summary RR: 2%

Cetuximab in Triple Negative MBC

Translational Breast Cancer Research Consortium (TBCRC) 001



- Primary endpoint: objective response
- Secondary endpoints: TTP, biomarker correlation with toxicity and response, OS
- Cetuximab-alone arm failed to meet predetermined response criteria and was closed
- Only arm 1a (cetuximab alone) and arm 1b (cetuximab alone, then cetuximab + carboplatin on progression) reported

Carey. *SABCS*. 2007 (abstr 307).

TBCRC 001: Patient Characteristics

- 68% with visceral disease
- Line of therapy and prior rx
  - 46% 1st line
  - 54% 2nd/3rd line
  - 83% prior anthracycline
  - 64% prior taxane
- 44% EGFR+

Cetuximab in Triple Negative MBC: Clinical Efficacy

Best Response	Cetuximab Alone (n=31)
CR	0
PR	2 (6%)
SD	5 (16%)
Clinical Benefit	3 (105)

Carey. *SABCS*. 2007 (abstr 307).

TBCRC 001: Clinical Efficacy

Includes patients initially treated with cetuximab and then treated with combination at time of progression

ITT population

	Arm 2 (N=71)	Arm 2 + 1b (N=95)
CR	**1 (1.4%)**	**1 (1%)**
PR	**11 (15%)**	**15 (16%)**
SD	**16 (23%)**	**22 (23%)**
PD	**37 (52%)**	**49 (52%)**
NE	**6 (8%)**	**8 (8%)**
RR	***17%***	***17%***
CB	***31%***	***29%***

Four patients on study Rx at 35, 39, 43, 99 weeks (1CR, 2PR, 1SD)

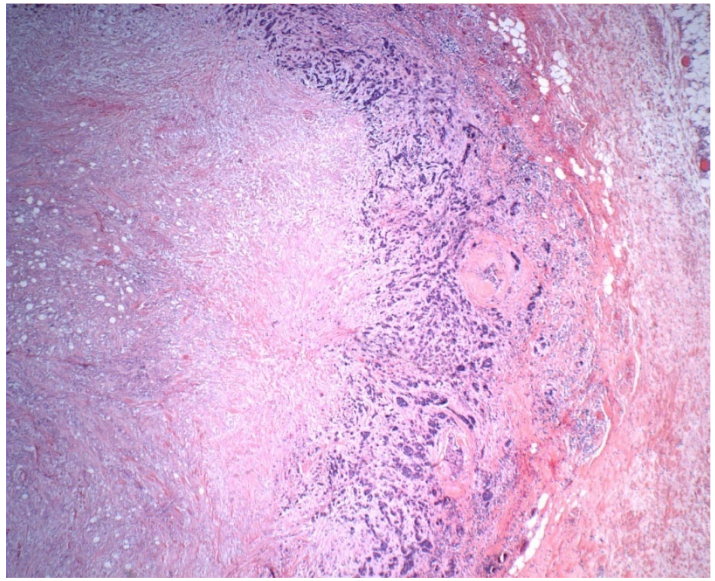
No relationship of line of therapy and likelihood of clinical benefit

CB=PR or SD≥24wks

Carey et al, ASCO 2008

Shared Characteristics of Sporadic Basal-like Tumors and BRCA1 -/- Tumors

- **ER^- PR^- Her2/Neu non-amplified**
- **Co-Cluster by Gene Profiling**
- **p53 mutant status**
- **Cytokeratin Expression**
- **Chromosome X Inactivation**
- **Genomic Instability**



Pathologic Features

High Grade

Central Necrosis

Pushing Borders

Lymphocytic Infiltrate

DF/HCC SPORE: Neoadjuvant Cisplatin (CDDP) in Triple-Negative Breast Cancer

- **N = 28**
  - **≥ 2-cm stage II/III triple negative**
- **Single-agent cisplatin 75 mg/m² q3w x 4 cycles prior to surgery**

Grade 4	
↑ LFT	1 pt
Grade 3	
Neutropenia	2 pts
Tinnitus	1 pt
Nausea	1 pt
Fatigue	1 pt
Hyperkalemia	1 pt
↑ LFT	1 pt

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

Young age correlated with path CR p=0.04

2 patients with BRCA1 mutation, both with Path CR

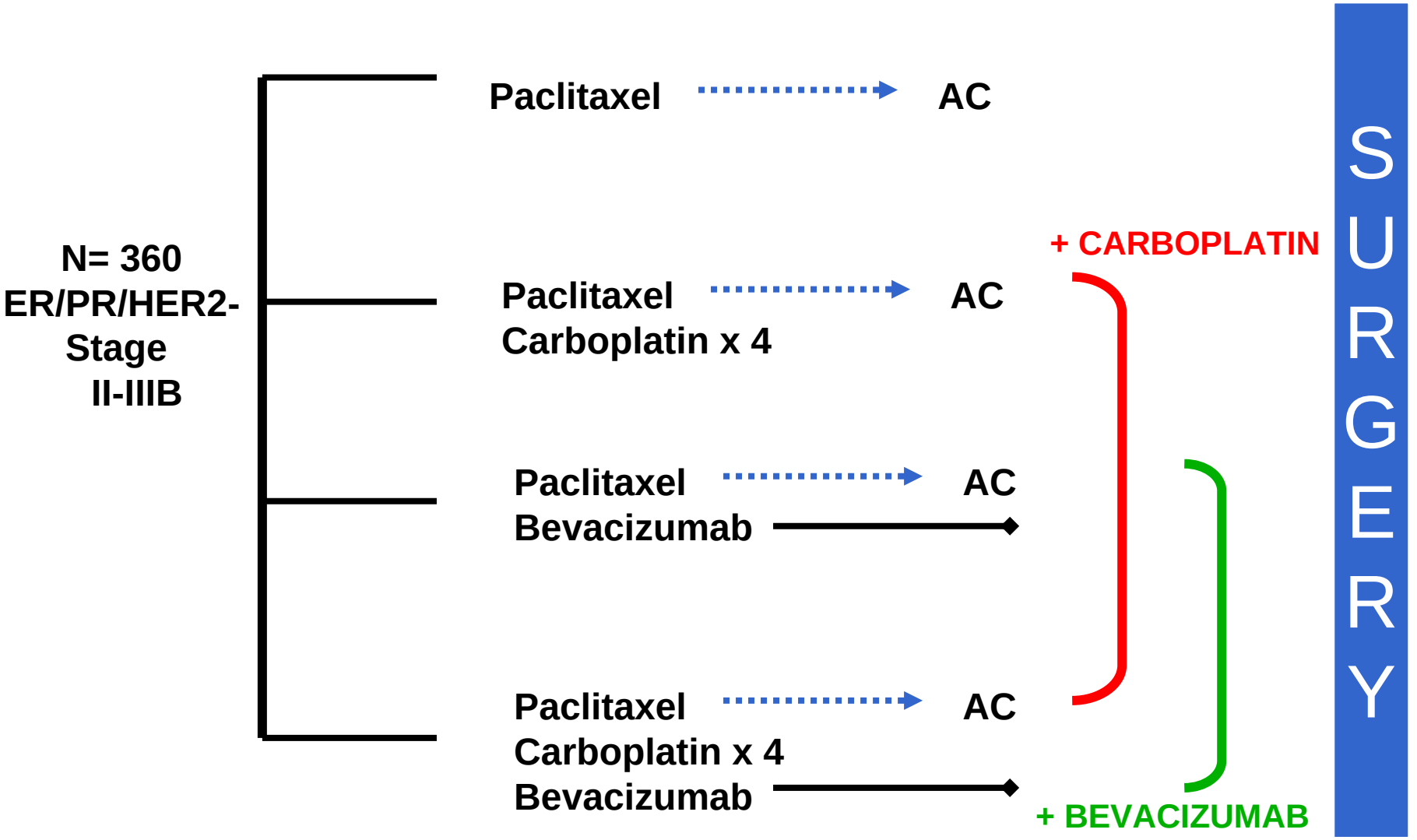
Garber *et al* Abs 3074, SABCS 2006

Cisplatin in Preop Setting in Patients With BRCA1-Related Breast Cancer

- **Narod and colleagues studied neoadjuvant response to cisplatin in 10 patients with BRCA1 mutations**
- **Same regimen as in Garber trial**
- **9/10 complete pathologic responses**
- **10th patient did not complete neoadjuvant therapy**

Byrski, T. et al., Breast Cancer Res Treat, Published online: 23 July, 2008

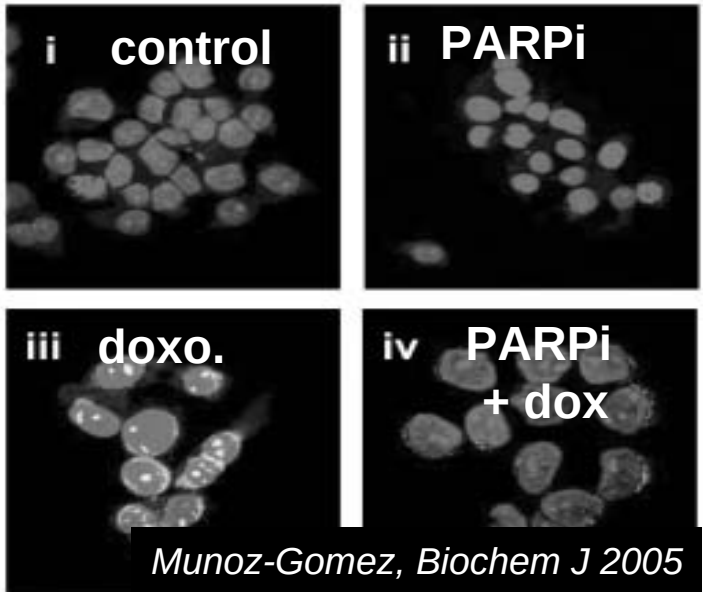
CALGB Triple Negative Neoadjuvant Trial Schema



The Potential Role of PARP Inhibition

- Loss of BRCA 1 or 2 → increased PARP dependence for DNA repair
- ? Augment efficacy of DNA-damaging agents
- PARP inhibitors are in clinical trials for both BRCA1 and Triple Negative

Cell Death Increased When PARP Inhibitor Added to Chemotherapy In BRCA2 Deficient Cells



Ongoing Studies PARP Inhibitors

- **Single agent trial of AZD 2281in patients with BRCA mutations**
- **Planned phase I of cisplatin plus AZD 2281**
- **Planned phase II of cisplatin plus AZD 2281 in preoperative setting for patients with triple negative disease**
- **Other agents in development from other companies**

Summary

- Molecular characteristics of triple negative and basal-like disease are a subject of active investigation
- More heterogeneity in this tumor subset than once imagined
- EGFR remains an interesting therapeutic target with very limited suggestion that it may be useful for a subset
- Exploitation of angiogenesis inhibition likely to be important
- Platinum salts *MAY* play a role
- PARP inhibitors are of great interest, particularly in triple negative, BRCA1/2 associated disease