National Cancer Institute

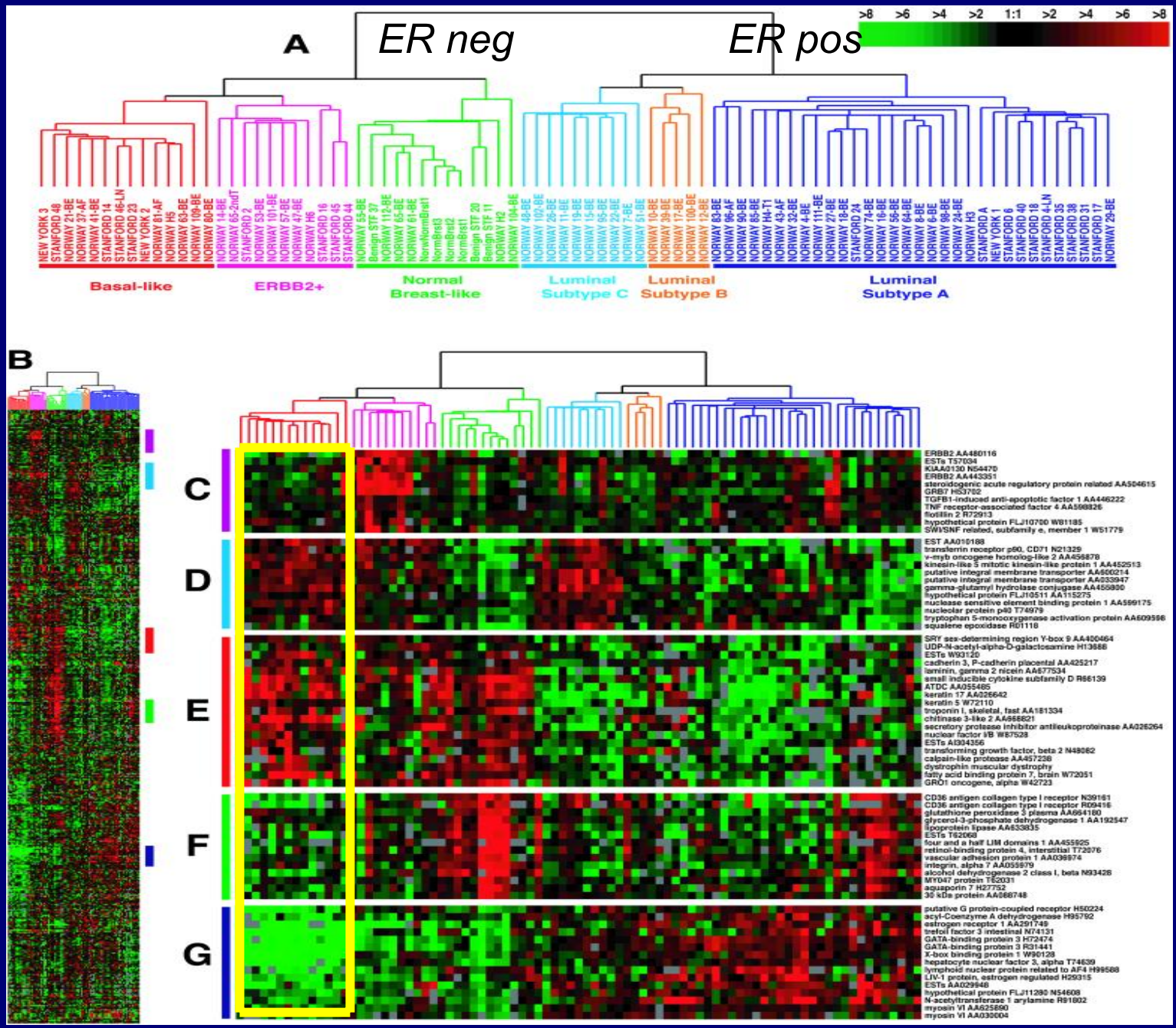
PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

Preoperative Treatment of the Triple-Negative (Basal Phenotype) Breast Cancer

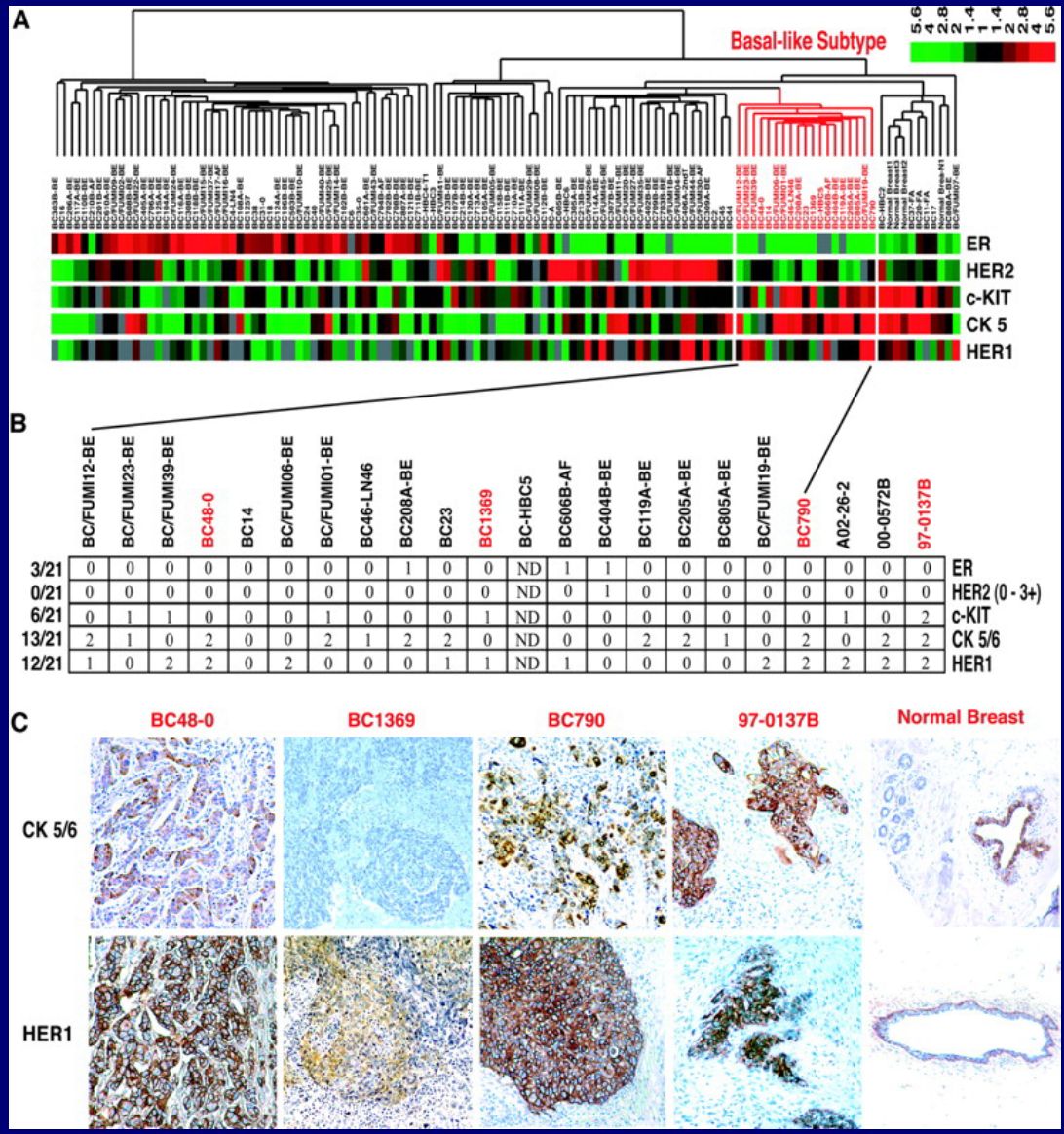
Judy E. Garber, MD MPH
Dana Farber Cancer Institute
Boston, MA 26 March 2007

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health



Sorlie, et al. PNAS 2001

Gene Expression Profiles and IHC of Basal-like Breast Cancers



Nielsen, T. O. et al. Clin Cancer Res 2004;10:5367-5374

IHC Features of Basal-like v. Non-Basal-like Breast Cancers

	Basal-like	Non-Basal-like	P value
ER	14%	78%	--
ErbB2	0%	26%	--
CK 5/6	62%	14%	--
C-KIT	29%	11%	<0.001
EGFR	57%	8%	<0.001
P53 mutation	82%	13%	<0.001
P53 protein	51%	22%	<0.006
Cyclin E	80%	17%	<0.001
Vimentin	94%	6-8%	0.001

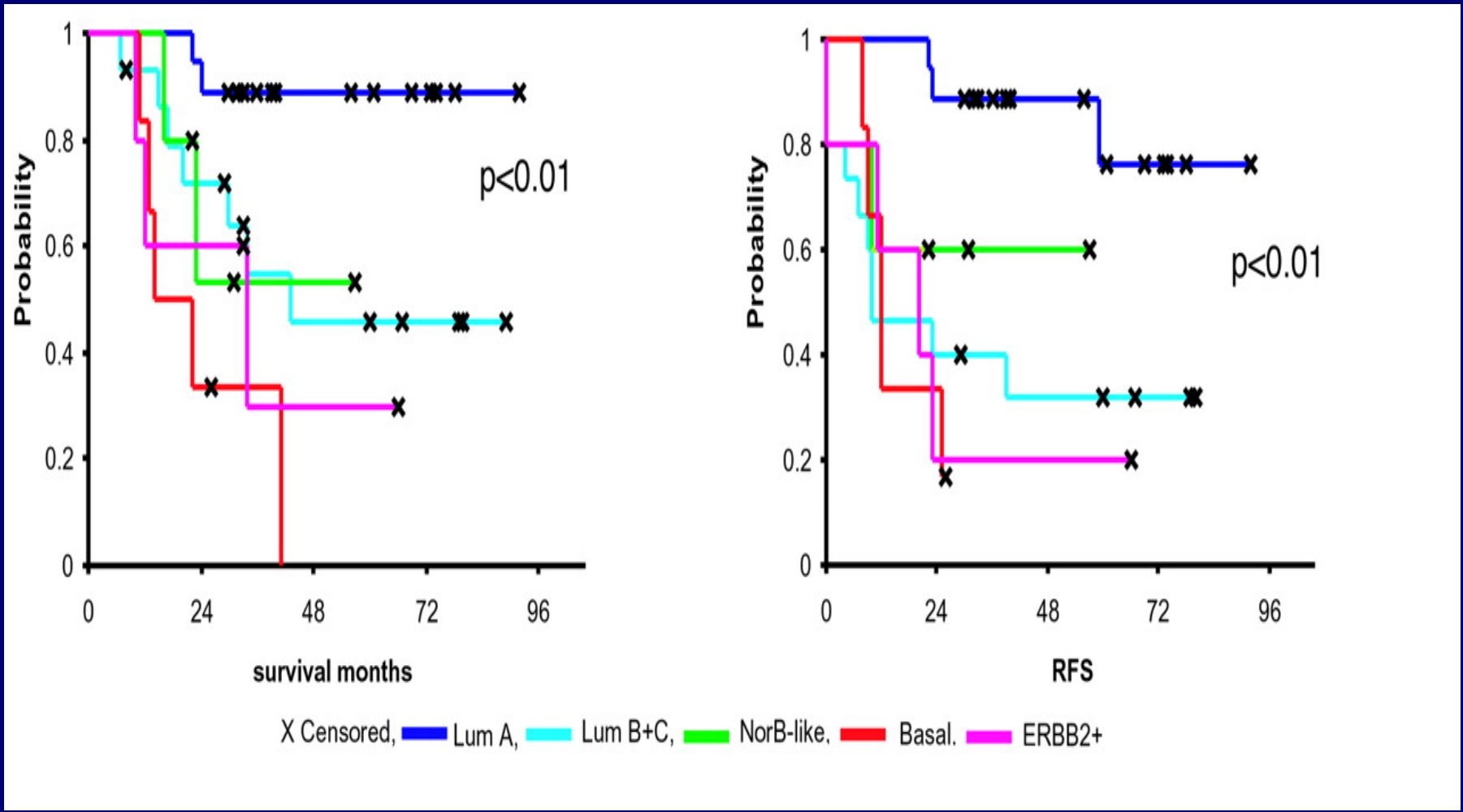
Cleator S et al. Lancet Oncology 2007;8:235-244

Risk Factors By Subtype

	Basal-like (n=95)	HER2+/ER- (n=61)	Luminal A (n=552)	Luminal B (n=48)
Menarche* (per 2y↑)	**0.78 (0.68-0.89)**	**1.14 (0.86-1.50)**	**0.90 (0.95-1.08)**	**0.98 (0.75-1.28)**
No births 1	2.36 (0.43-13.01)	1.50 (0.19-11.77)	0.50 (0.24-1.06)	0.91 (0.09-8.83)
≥2	1.80 (0.37-8.85)	1.15 (0.17-7.63)	0.42 (0.21-0.84)	0.56 (0.07-4.56)
Age FTB	0.95 (0.71-1.27)	0.87 (0.60-1.05)	1.08 (0.95-1.23)	1.04 (0.70-1.55)
Menopause	1.02 (0.82-1.28)	1.09 (0.81-1.46)	1.13 (1.01-1.28)	1.10 (0.78-1.57)
BMI premen* (per 5kg↑)	**1.18 (0.86-1.64)**	**0.53 (0.25-1.12)**	**0.71 (0.57-0.88)**	**0.88 (0.48-1.60)**
BMI postmen	0.87 (0.66-1.14)	0.97 (0.73-1.28)	1.00 (0.90-1.12)	1.02 (0.74-1.42)
FHx	3.17 (1.69-5.92)	2.35 (1.03-5.38)	1.72 (1.21-2.45)	2.31 (0.88-6.88)

Yang XR et al, CEBP 2007

Overall and Relapse Free Survival Based on Tumor Subclasses Defined with Gene Expression Patterns



Sorlie, et al. PNAS 2001

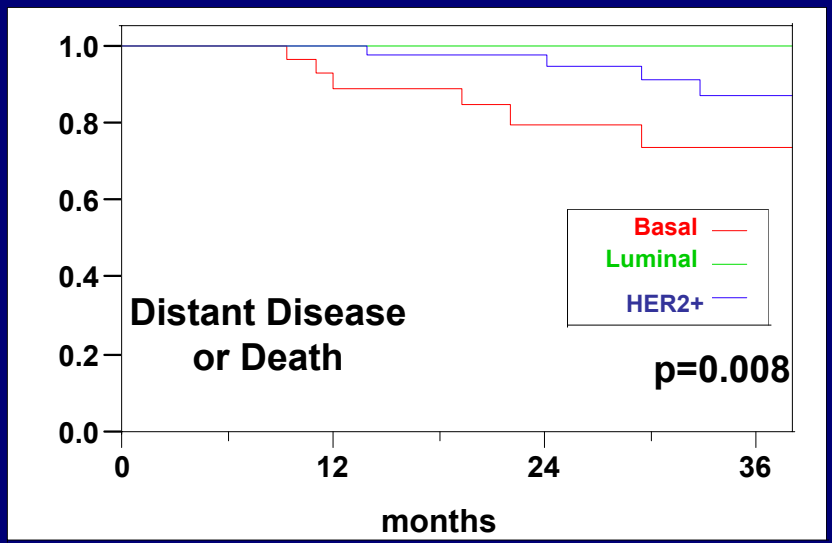
Correlation and Molecular Classification and Pathologic CR

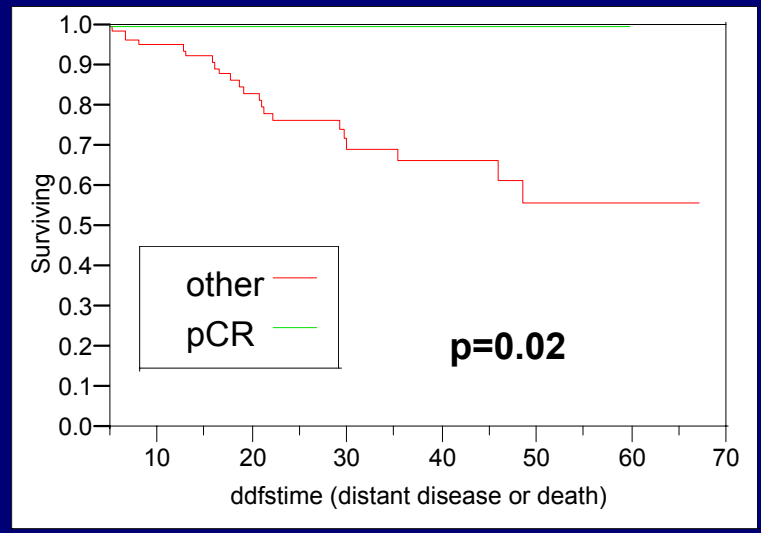
Subtype	T-FAC (n=82)	AC-T^2 (n=108)
Luminal A/B	2/30 (7%)	4/62 (7%)
Normal breast-like	0/10 (0%)	N/A
erbB2+	9/20 (45%)	4/11 (36%)
Basal-like	10/22 (45%)	9/34 (26%)
	p<0.001	p=0.003

Rosier R et al. Clin Cancer Res 2005;11:5678-5685
Carey L et al. Clin Cancer Res, in press

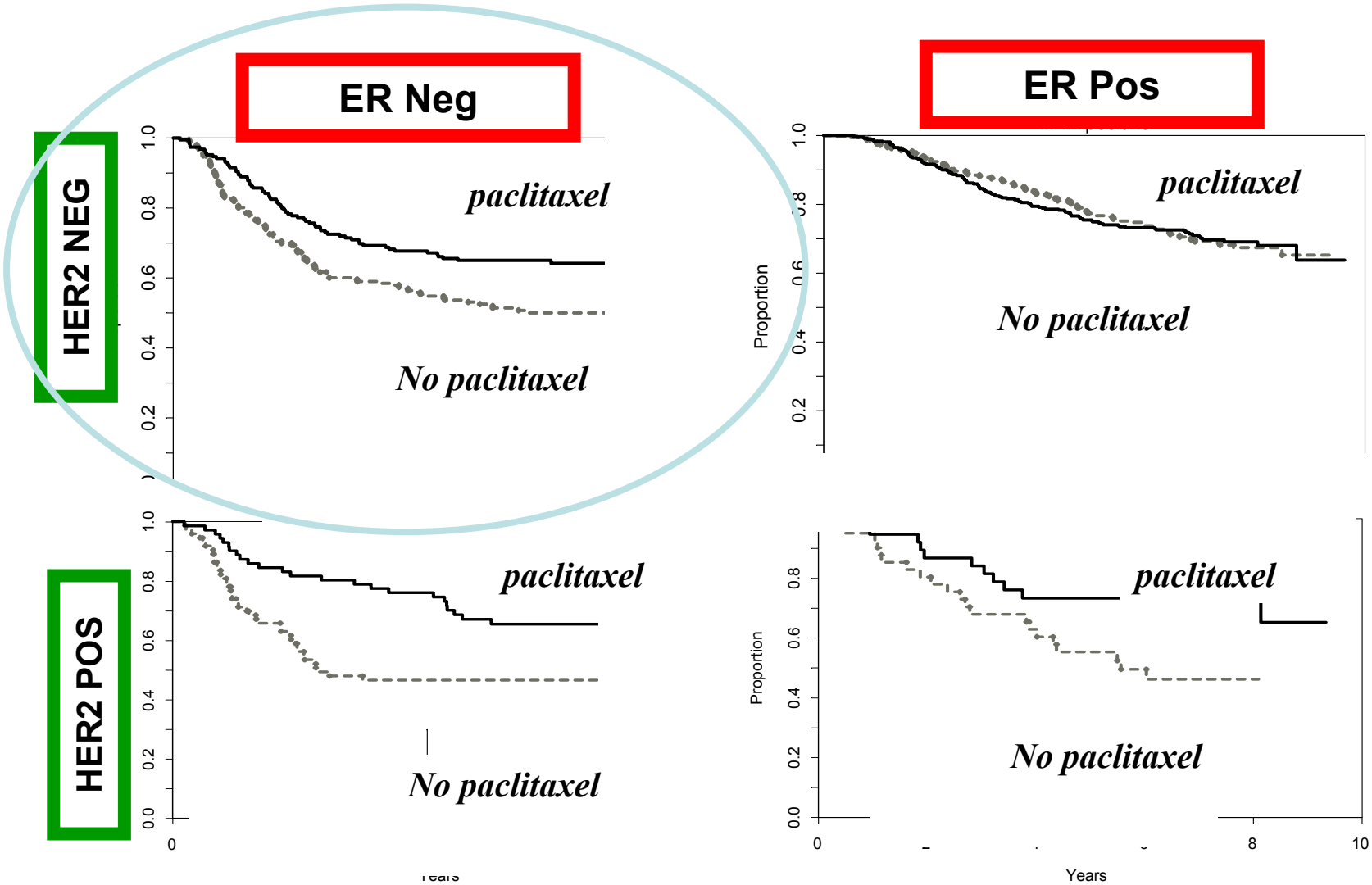
Intrinsic Subtypes and AC-T Sensitivity (Lisa Carey – UNC)

Response to Neoadjuvant Anthracycline and Taxane	Basal-like (n=33)	HER2+/ER- (n=55)	Luminal (n=36)
Clinical Response (CR+PR)	76%	65%	51%
Path CR	24%	18%	5%



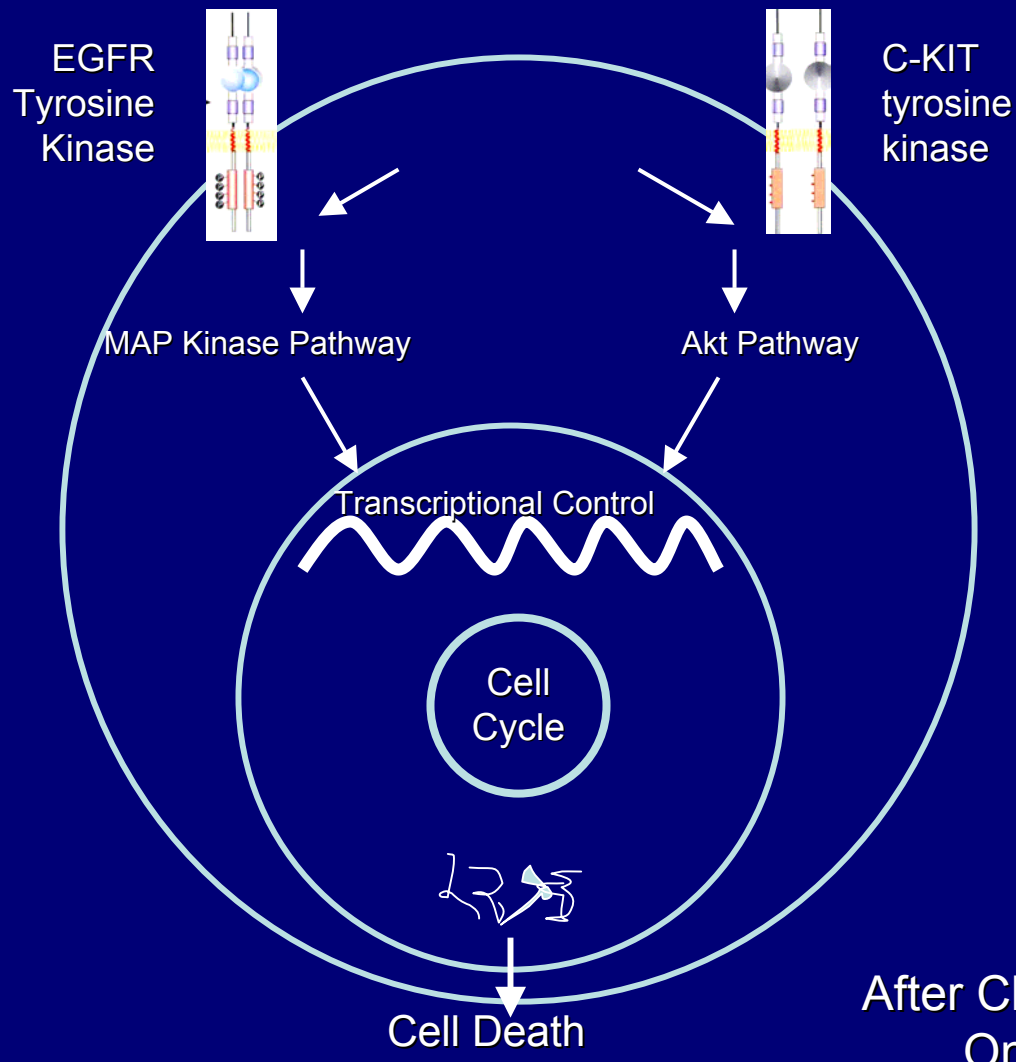


C9344 Disease-free Survival by ER and HER2



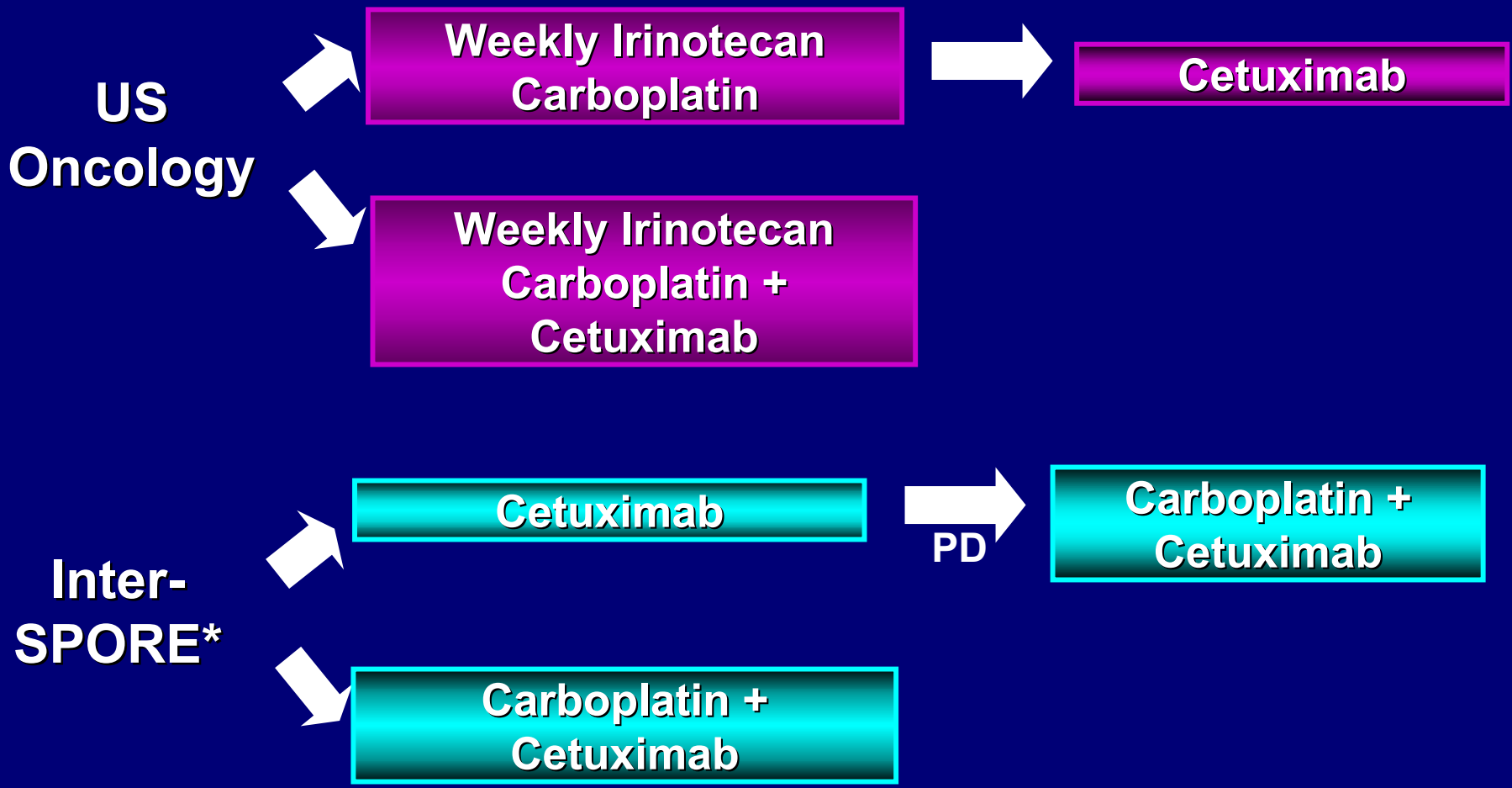
Hayes, ASCO 2006

Triple-negative carcinoma: potential therapeutic targets



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

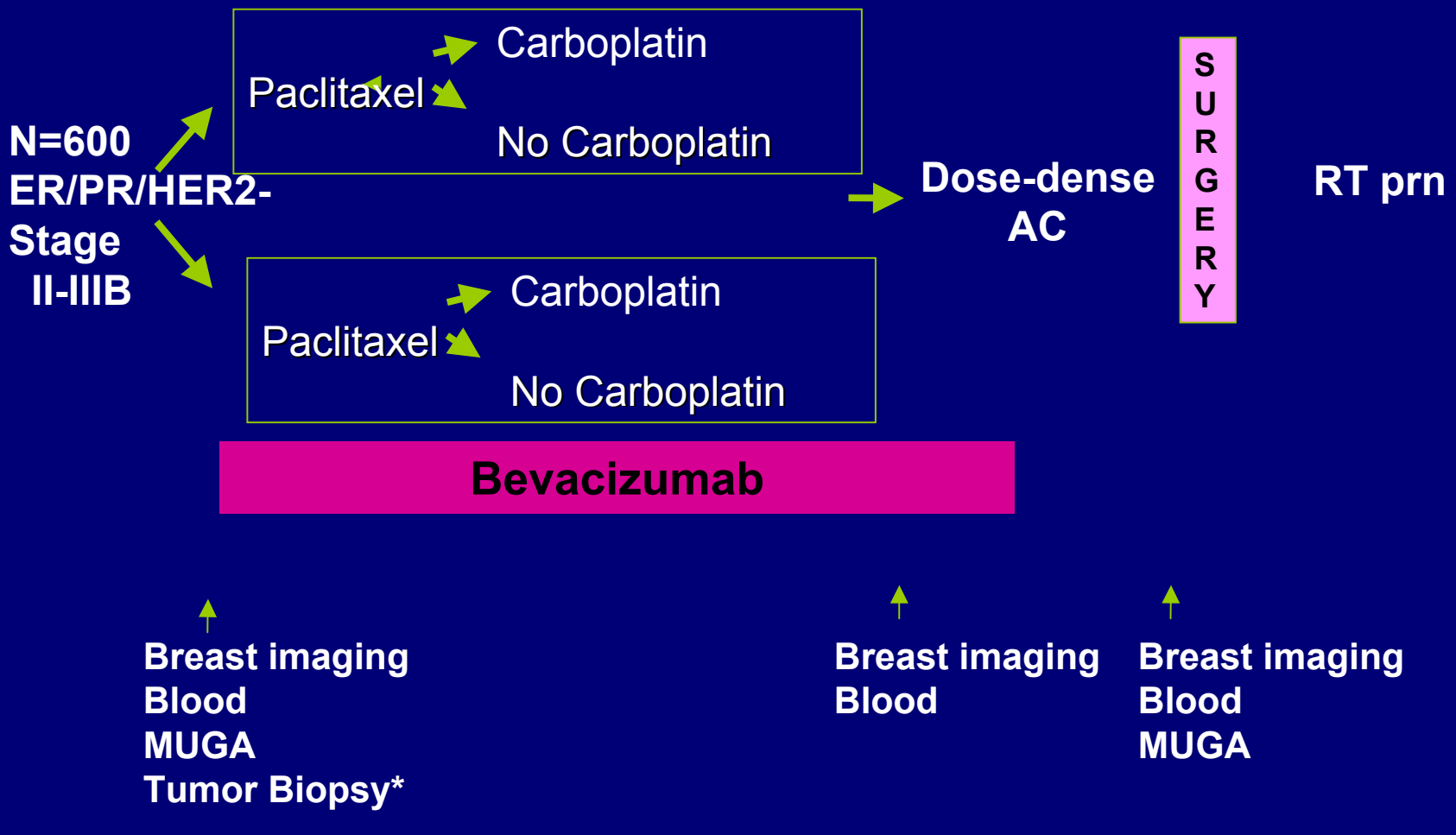
EGFR-Targeting Trials in Stg4 Triple Negatives



*UNC, UCSF, DFCI, UAB, IU, Mayo, JHU, GT, Baylor, Duke, MDACC, Wash U

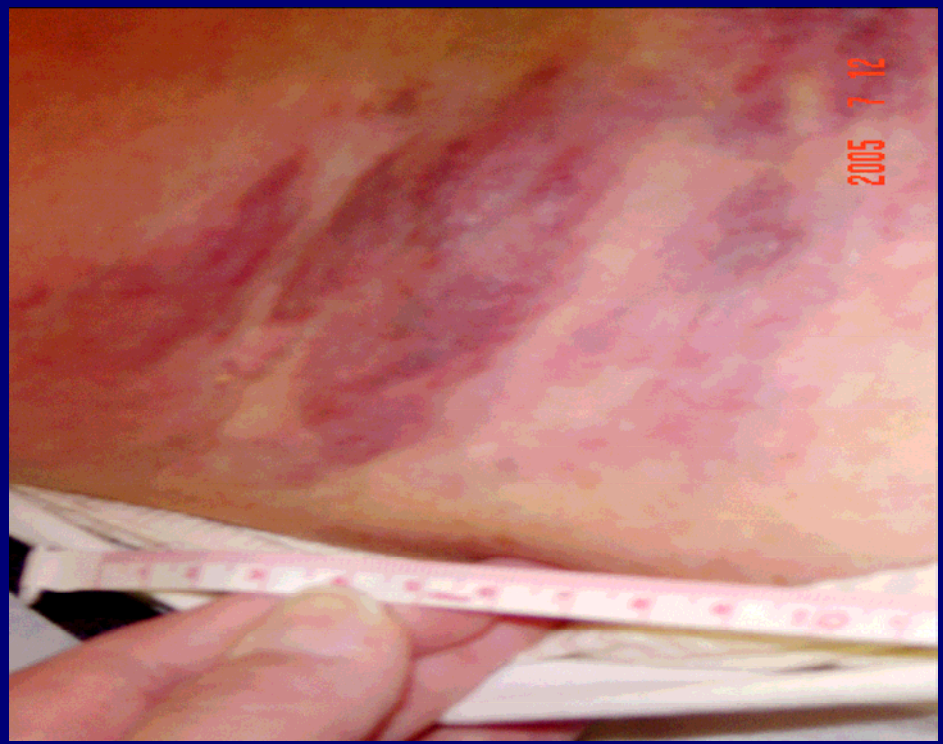
Proposed CALGB Triple Negative Neoadjuvant Trial Schema

W Sikov, PI

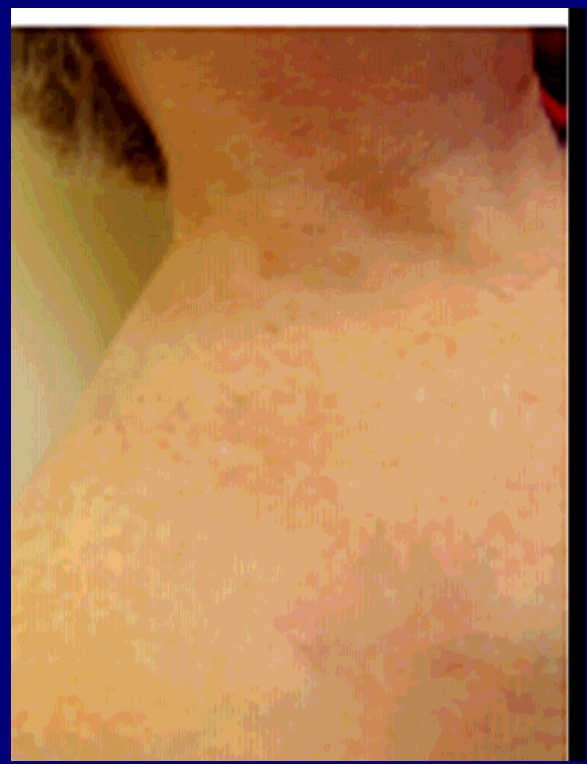


Phase I Trial of UCN01 and Irinotecan in Resistant Solid Tumors

2 Partial Responses in ER/PR/HER2 Negative Breast Cancer Pts



Pre-study Photograph of Local Disease



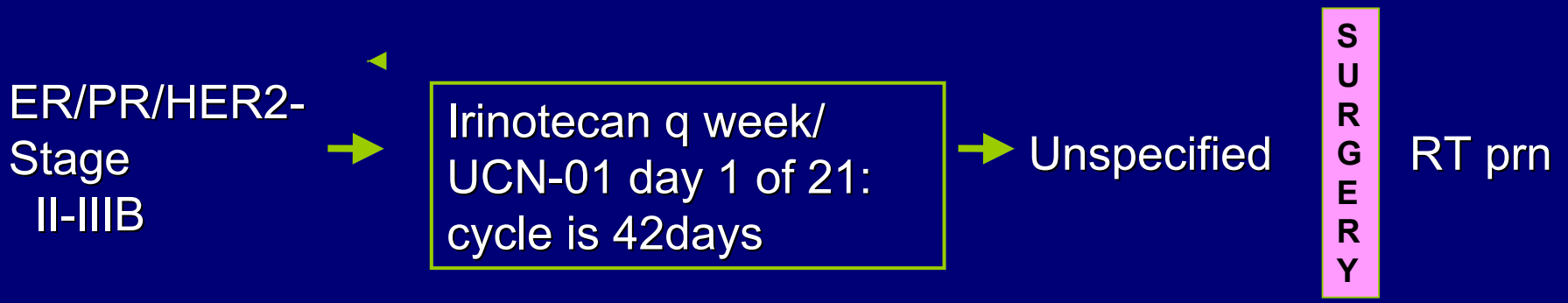
After 2 Cycles of Therapy

CTEP Extension for TNBC Trial

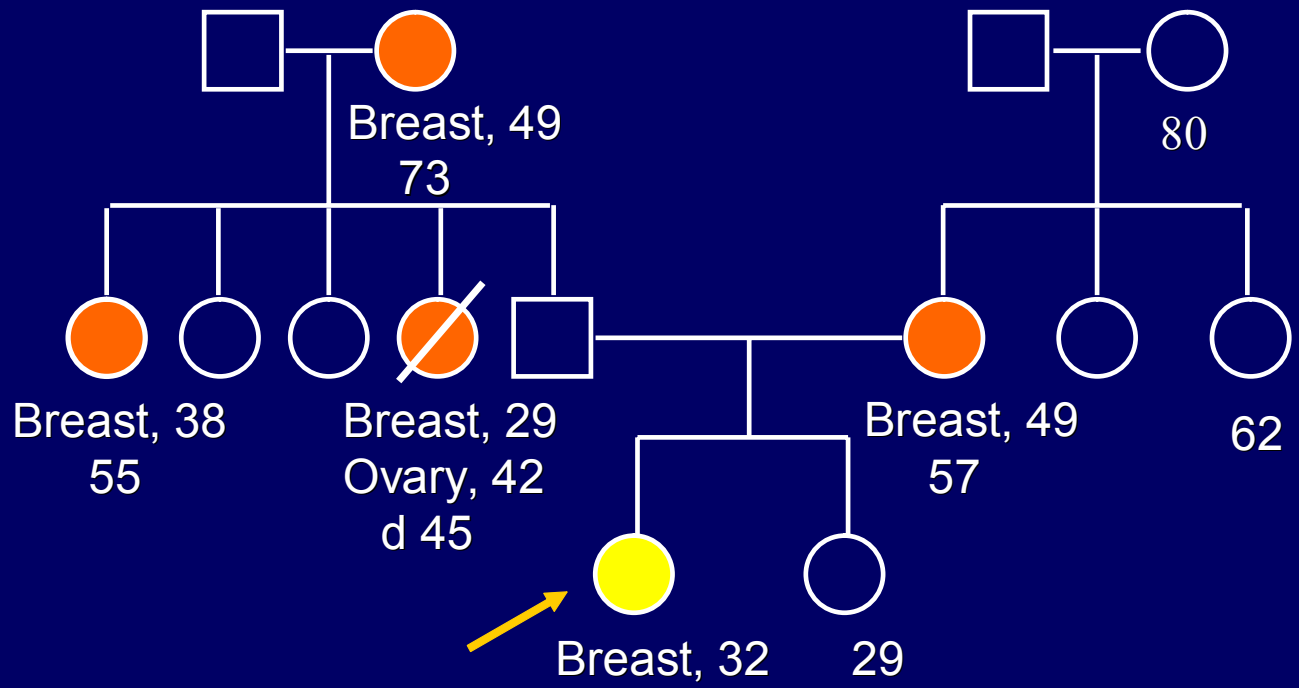
PM Fracasso et al., Siteman Cancer Center, Washington University, St. Louis MO

Proposed Trial: UCN01 and Irinotecan in Triple Negative Breast Cancers

P Fracasso, H Pwinica-Worms



A Classic Hereditary Breast/Ovarian Cancer Kindred



BRCA1 and BRCA2: Caretaker Genes

Maintenance of genomic integrity through:

- DNA damage recognition and repair
- Transcriptional regulation of gene expression
- Chromatin remodeling
- Cell cycle checkpoint control

Venkitaraman AR. *Cell.* 2002;108:171-182.

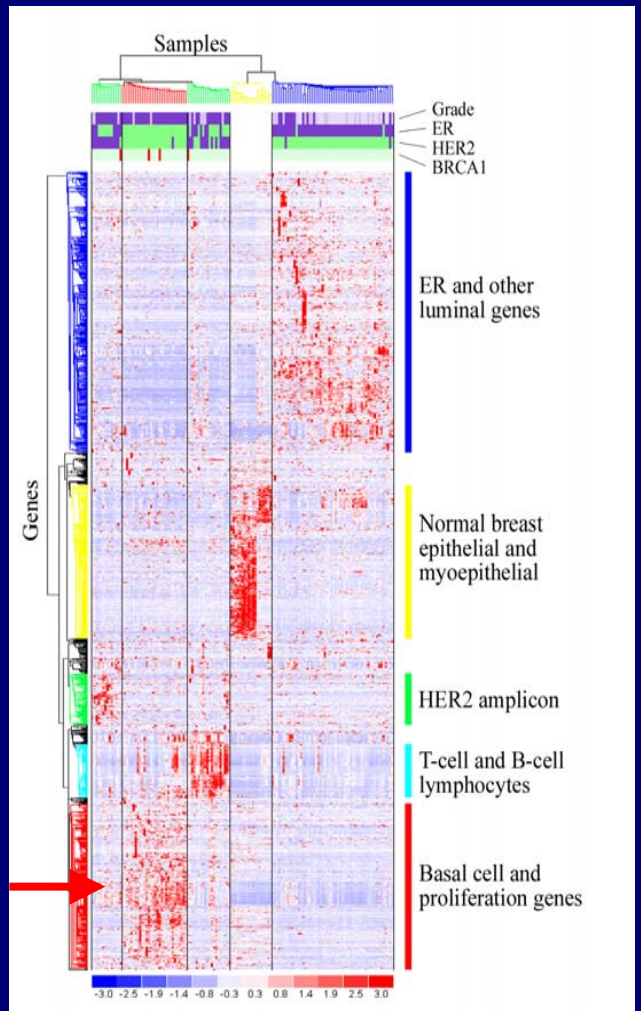
% ER+ Breast Cancers in *BRCA1/2* Carriers by Age at Diagnosis

Class	N (%)	ER+%	p[a]
BRCA1			
Age <45	59 (24.7)	19.0	
Age 45-55	72 (30.1)	31.1	
Age 55-65	108 (45.2)	38.0	p=0.020
BRCA2			
Age <45	43 (48.8)	83.7	
Age 45-55	35 (39.8)	71.4	
Age 55-65	10 (11.4)	80.0	p=0.418

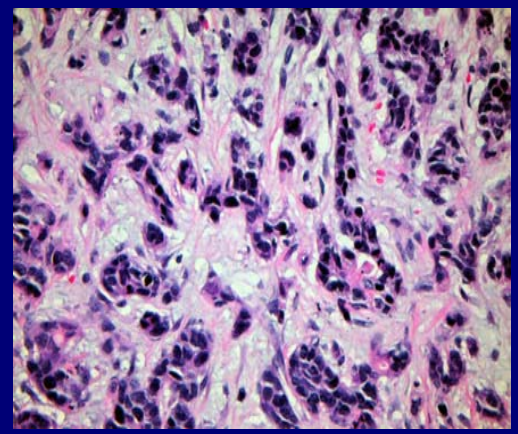
Foulkes WD *Clin Cancer Res* 2004:10;2029-34

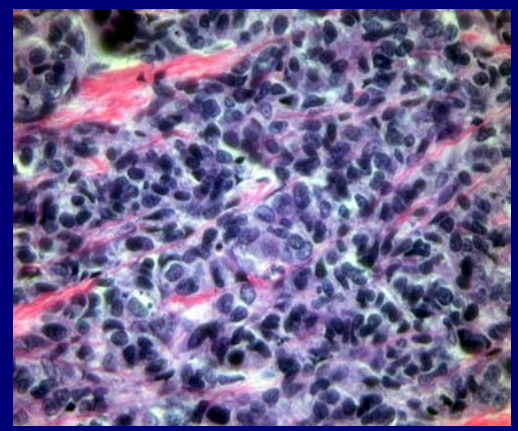
BASAL-LIKE BREAST CANCERS

80% of *BRCA1* mutation-associated cancers sort with the "basal-like" group of ER(-) breast cancers



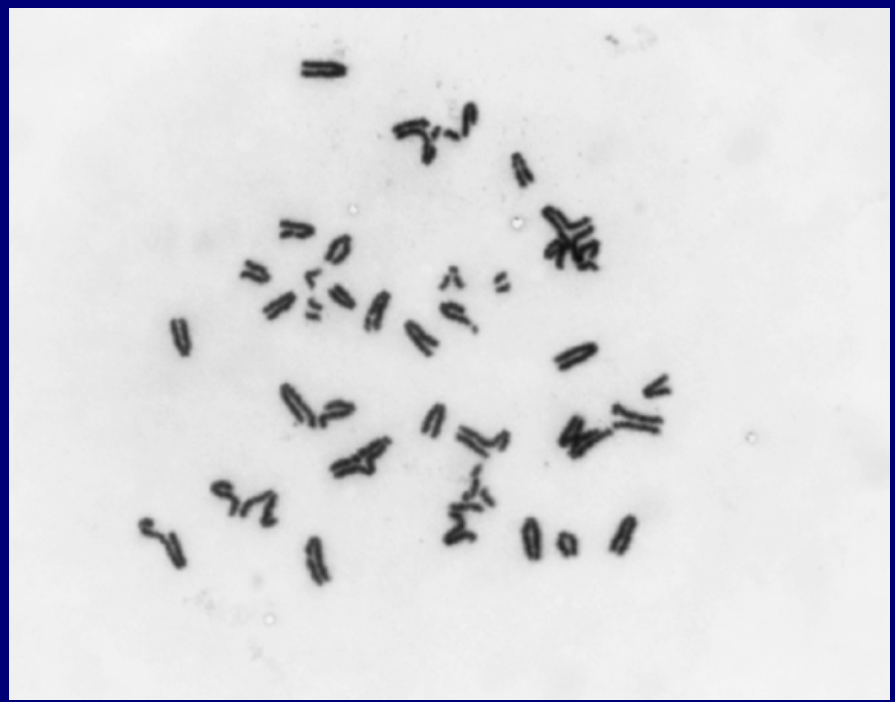
- 10% of breast cancers
- ER(-) PR(-) HER2(-)
- Poorly differentiated
- High grade, Aneuploid
- EGFR+, cyclin E+
- Express basal keratins CK5/6; Vimentin
- Little DCIS
- Poor prognosis
- Different stem cell?

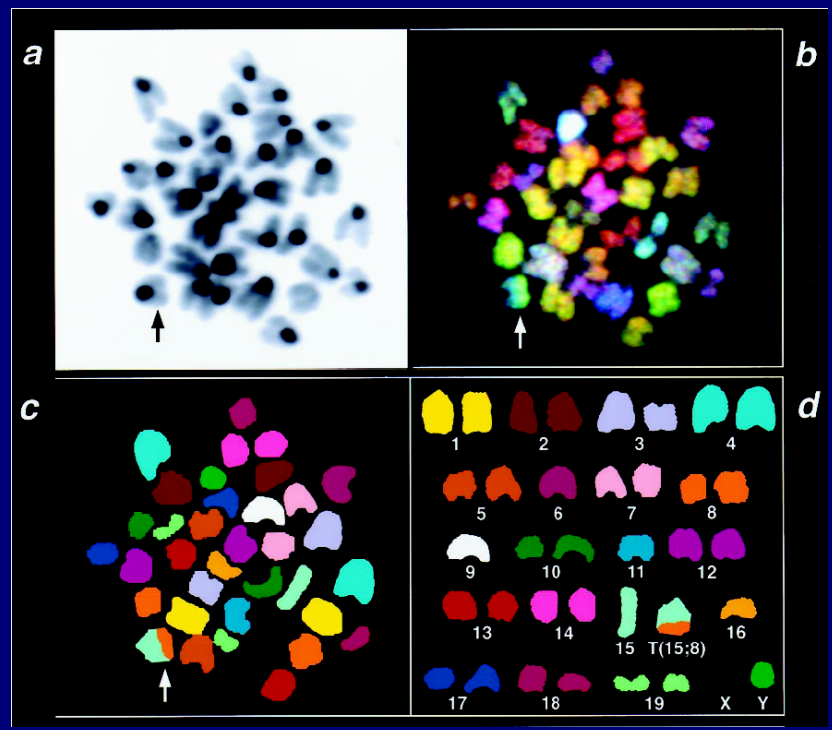




BRCA1-deficient cells develop gross chromosomal abnormalities with DNA damage

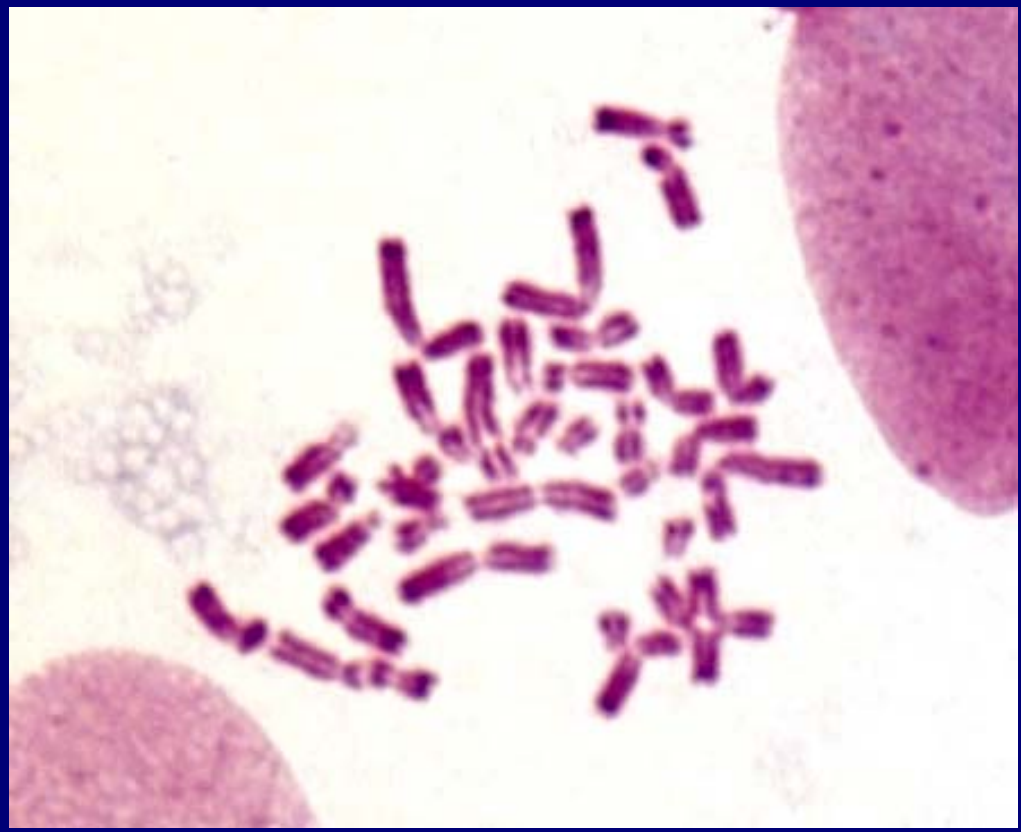
	Total # of metaphases	*% Abnormal*	*# of Embryos*
Brca1$^{+/+}$ or Brca1$^{+/-}$	97	3.1	4
Brca1$^{-/-}$	47	31.9	6
Brca1$^{+/-}$ p53$^{+/-}$	41	2.4	1
Brca1$^{+/-}$ p53$^{-/-}$	38	2.6	1
Brca1$^{-/-}$ p53$^{-/-}$	76	72.4	2





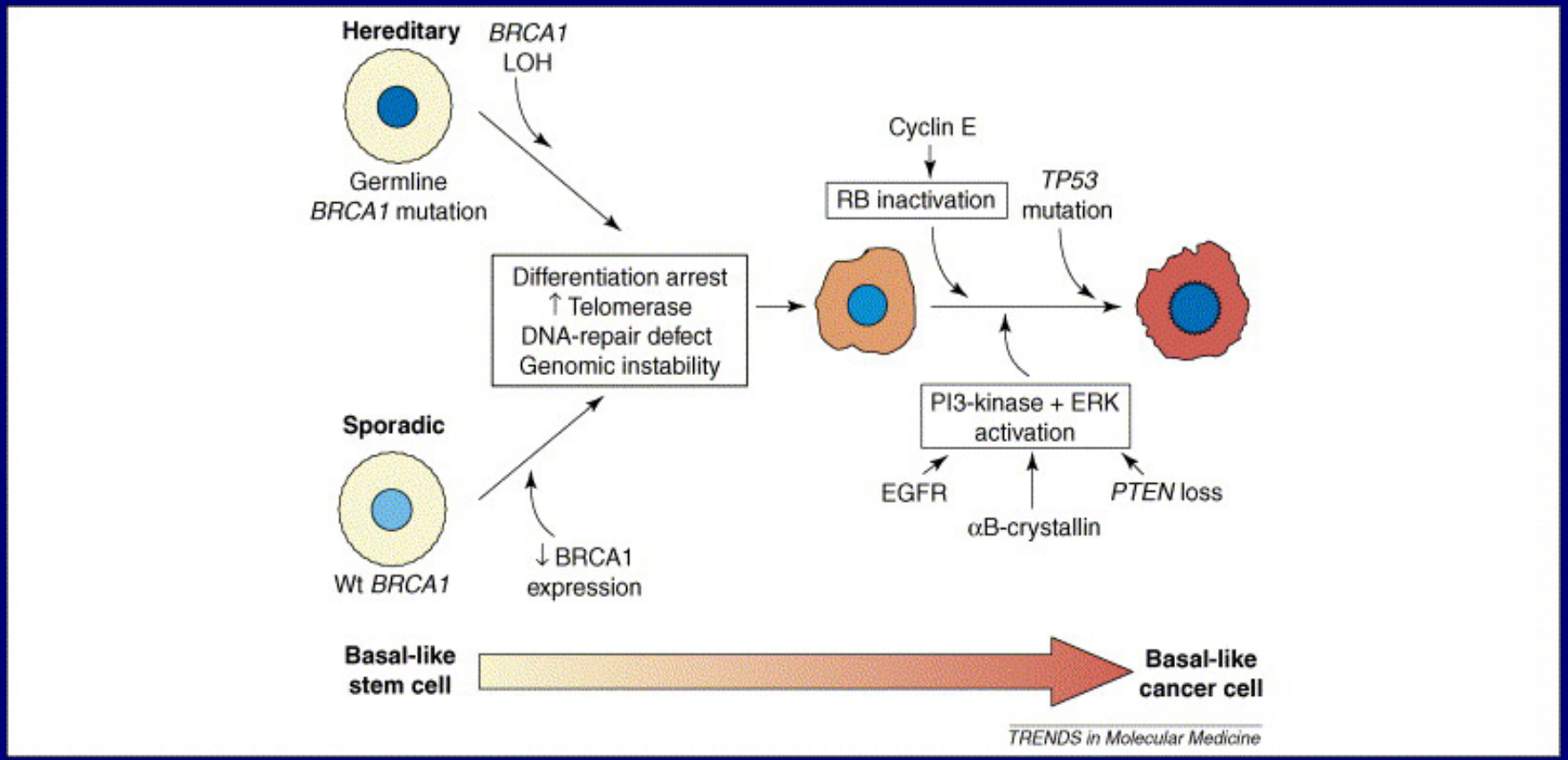
Shen et al, 1998

Basal-like Tumors Show DNA Damage Sensitivity



Permission of D Silver, MD PhD

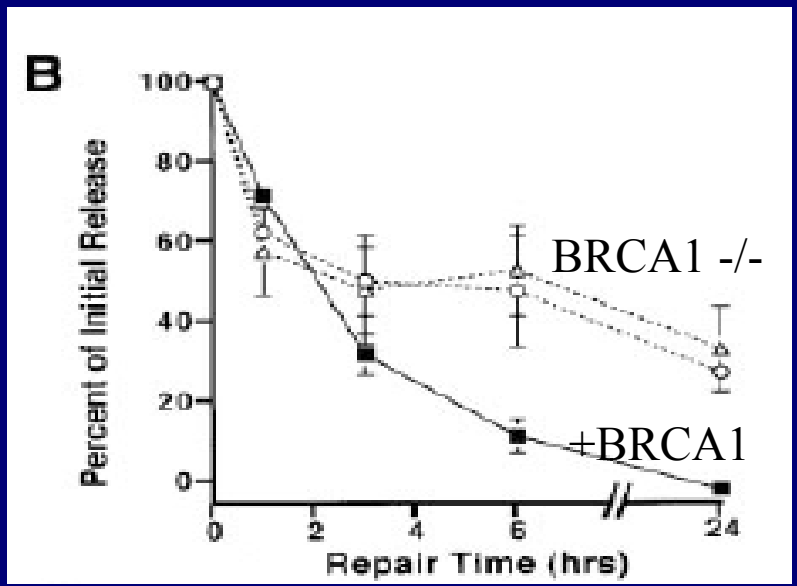
Working Model for BRCA1- and Sporadic Breast Cancer Pathogenesis



Yehiely F et al.Trends in Molec Med 2007;12:537-544.

BRCA1-Deficient Cancer Cells Have a Defect in DNA Double Strand Break Repair

γ-Radiation



Scully, Ganesan et al, Mol. Cell 1999

Mitomycin C

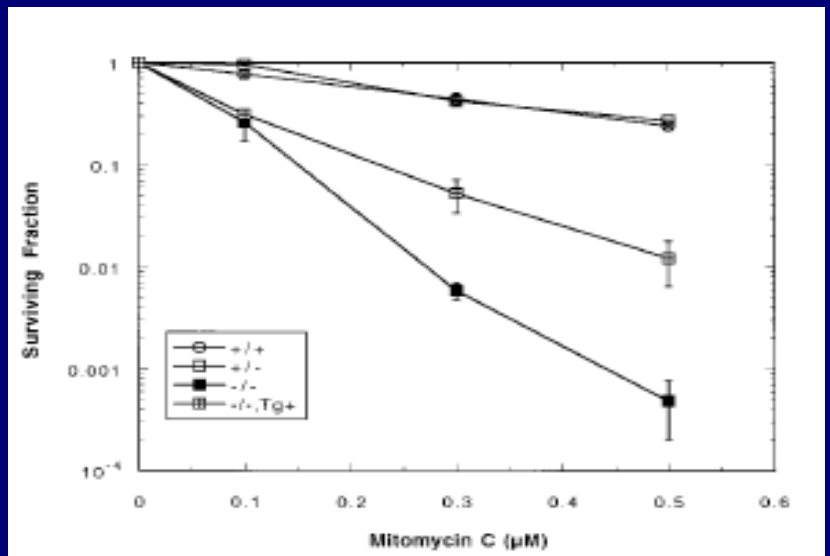
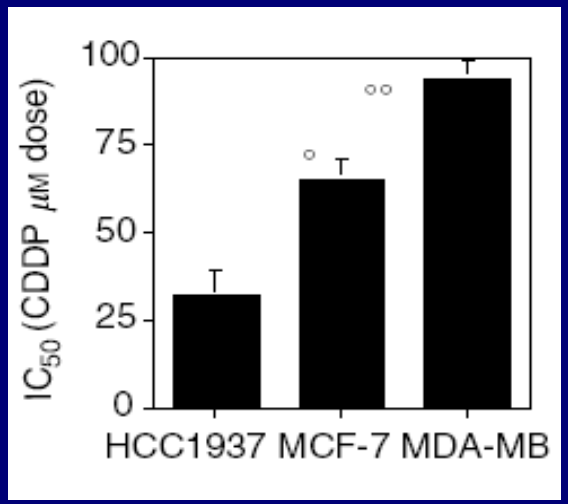


Fig. 3. Brca1$^{-/-}$ cells are hypersensitive to mitomycin-C. Clonogenic survival was assessed after treatment with varying concentrations of mitomycin-C. Four plates from each *Brca1* genotype, as indicated, were assessed for colony formation 8–10 days after exposure to mitomycin-C. The experiments were repeated. *Bars*, SE.

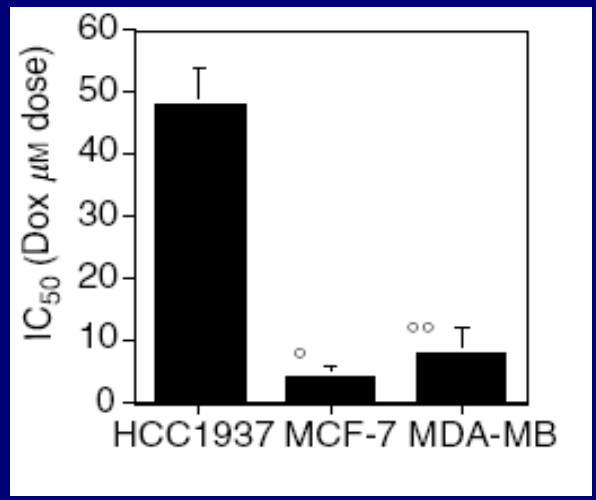
Moynahan et al, Cancer Res 2001

BRCA1-Deficient Cells Are Hypersensitive to Cisplatin

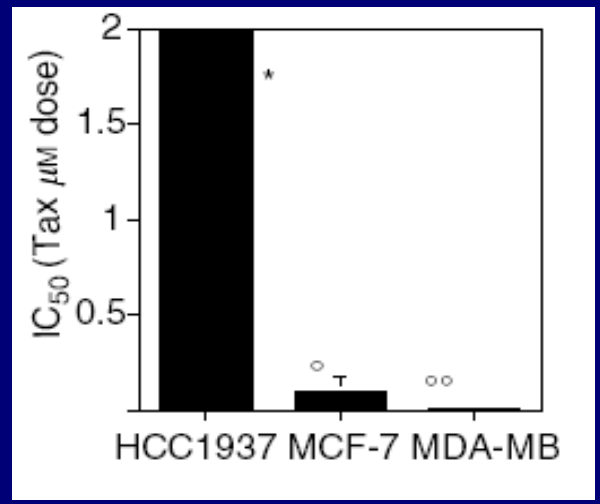
CISPLATIN

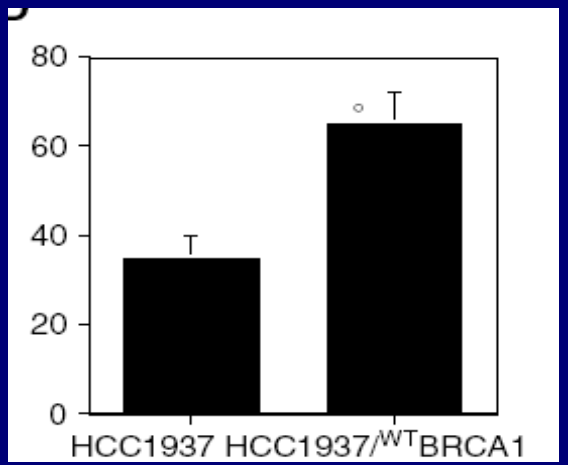


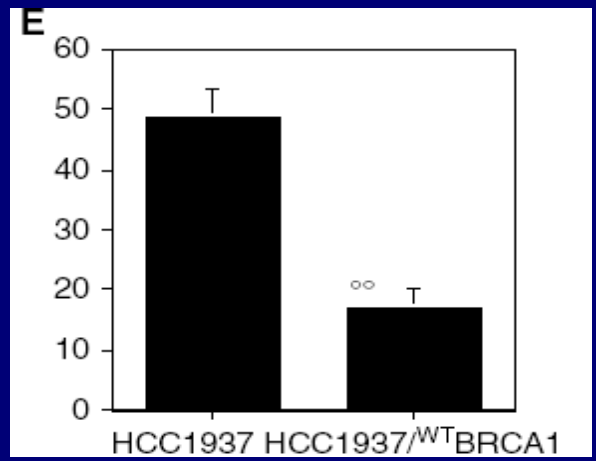
DOXORUBICIN

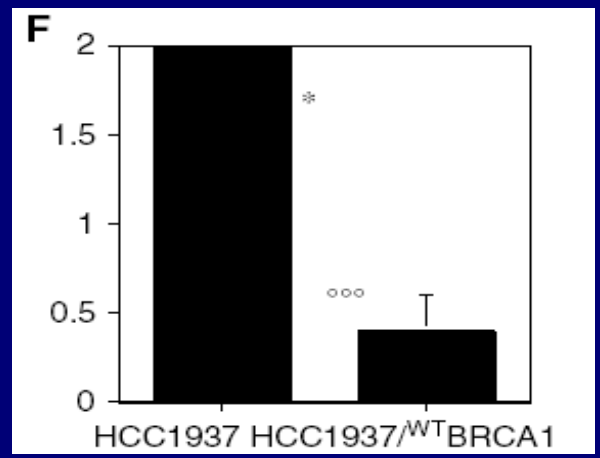


PACLITAXEL



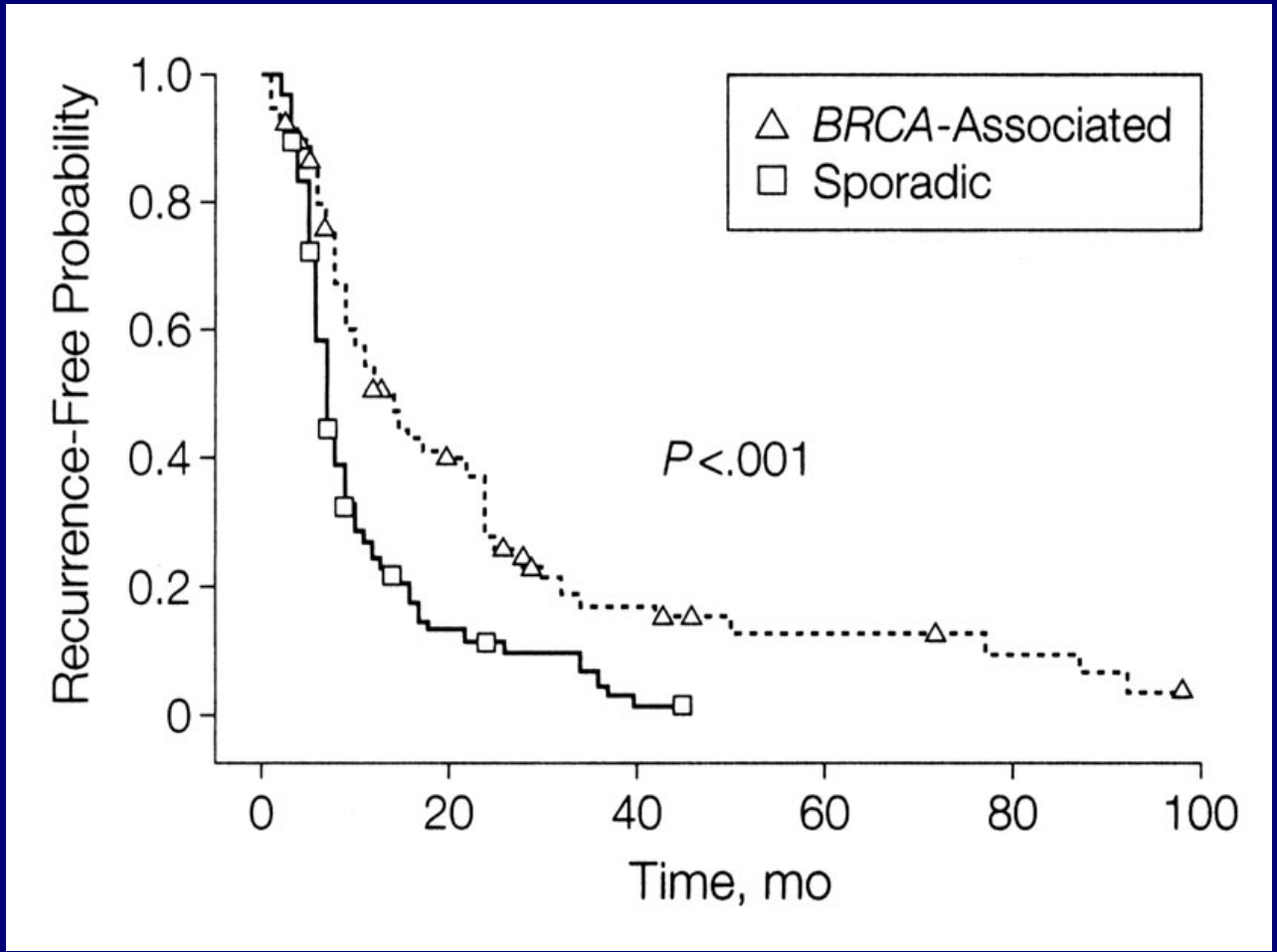






Tassone et al, 2003 BJC

Recurrence-Free Interval Probabilities in Patients with Advanced Ovarian Cancers



Boyd J et al. *JAMA* 283:2260, 2000

DF/HCC NeoAdjuvant Platinum in Triple Negative Breast Cancer

> 2cm, Stage II/ III
ER/PR/Her Neg
Breast Cancer on Core Biopsy

→

Cis Platinum
75mg/m2 q3wks
x 12 weeks*

→

Standard Adjuvant Therapy per MD

Tissue:

5q, 8q LOH

IHC: BRCA1, CK5/6

Microarrays: cDNA, SNP

FANCF methylation

Radiation damage assay

Blood:

BRCA1

Imaging

Mammo

US

MRI

* Additional MRI and Core bx after 1 dose of CDDP: radiation damage assay

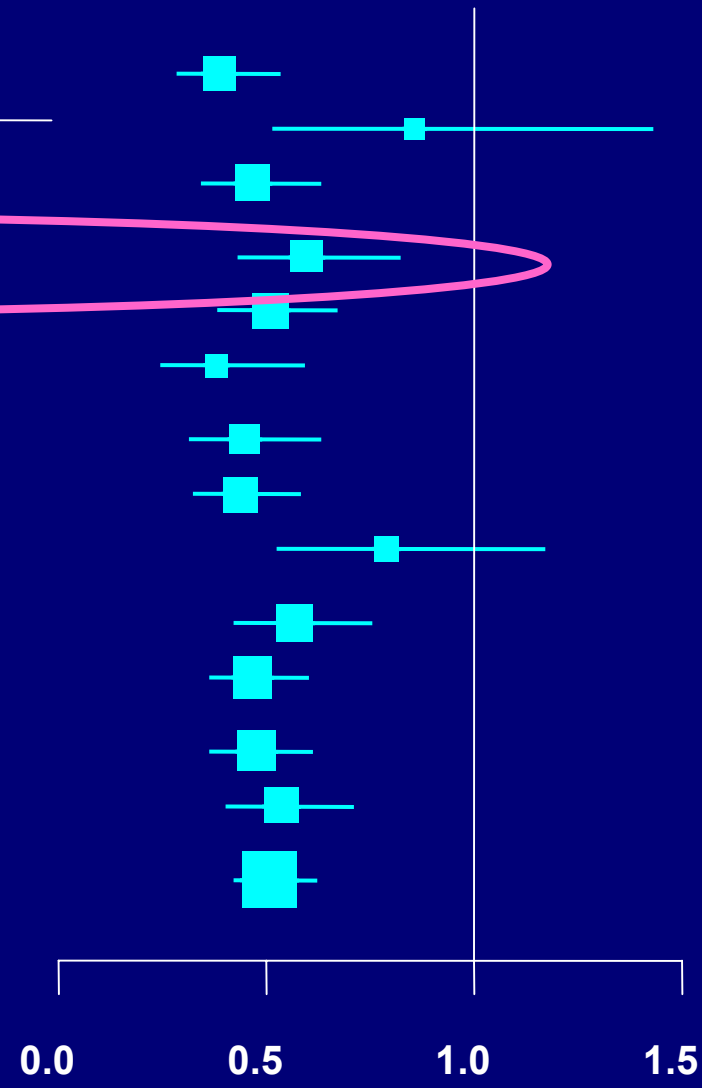
Responses to Neo-Adjuvant CDDP (n=28)

Response	Clinical	Pathologic
Complete	4 (14%)	6 (21%)
Partial	10 (35%)	4 (14%)
Stable	6 (21%)	9 (33%)
No Response	4 (14%)	5 (18%)
Progression	4 (14%)	4 (14%)
Grade 3 toxicity	1	

2 *BRCA1* carriers have had path CR: Age at Dx also significantly associated with response

Bevacizumab in Clinical Subsets

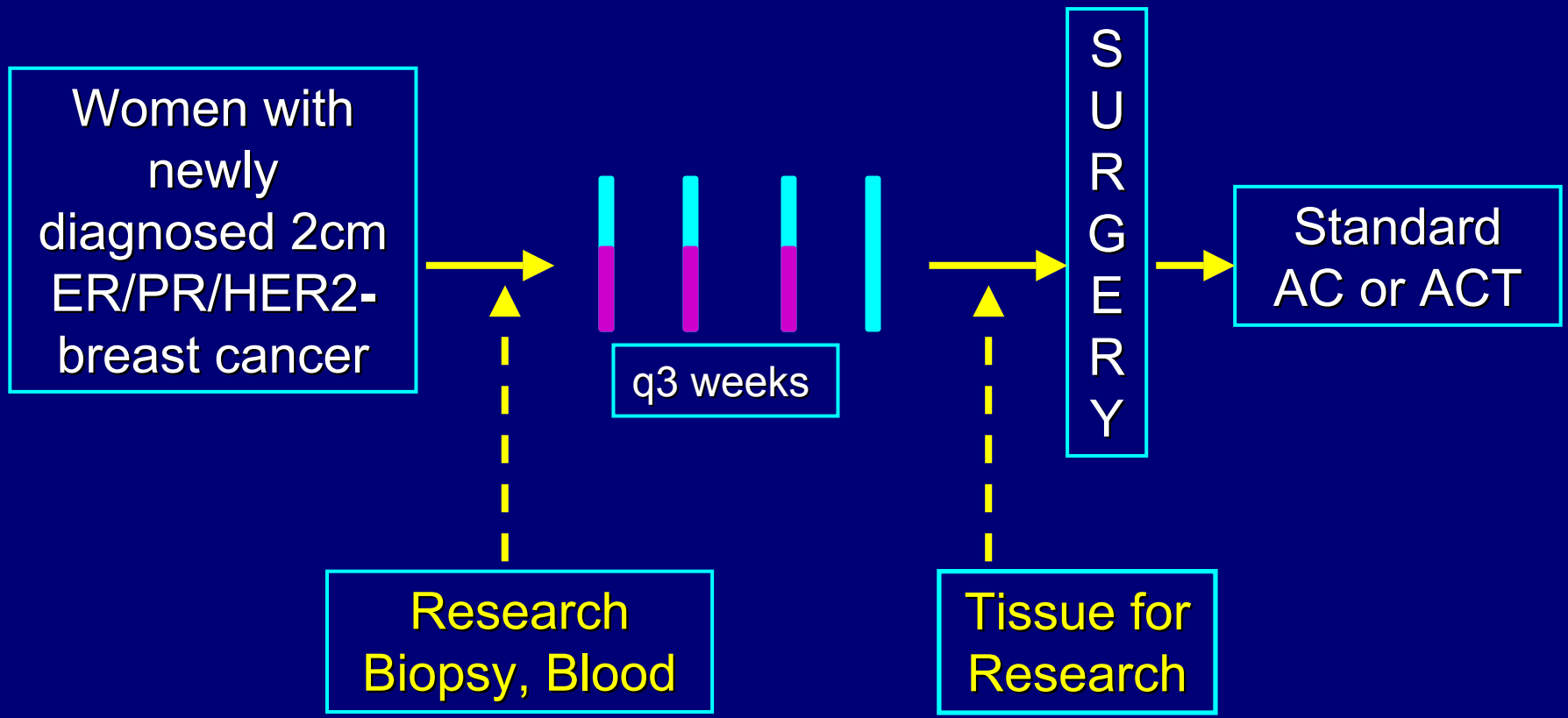
Group	Ratio	95% Conf Int	N
ER+, PR+	0.39	(0.29, 0.53)	200
ER+, PR-	0.86	(0.52, 1.43)	80
ER-, PR-	0.47	(0.35, 0.63)	184
No adj chemo	0.60	(0.44, 0.82)	178
Non-taxane	0.51	(0.39, 0.67)	234
Taxane	0.38	(0.25, 0.59)	86
Age 27 - 49	0.45	(0.32, 0.63)	155
Age 50 - 64	0.44	(0.33, 0.58)	232
Age 65 - 85	0.79	(0.53, 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, SABCS 05

Cisplatin plus Bevacizumab in Triple Negative Breast Cancer

PI: P Ryan, MD PhD MGH, DF/HCC

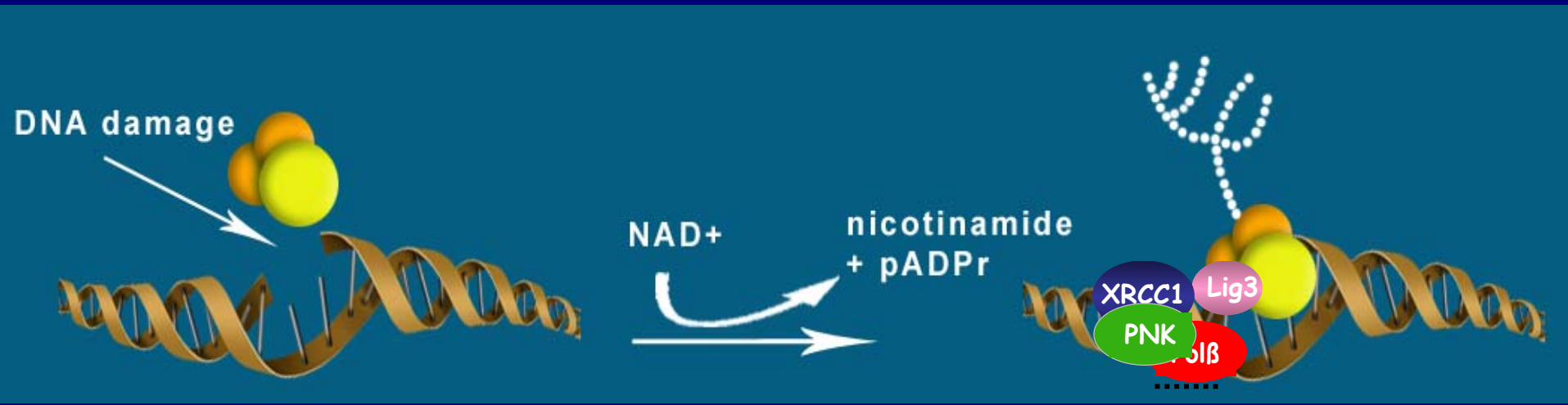


Poly (ADP-ribose) polymerase (PARP)

Involved in DNA base-excision repair

Binds directly to DNA damage

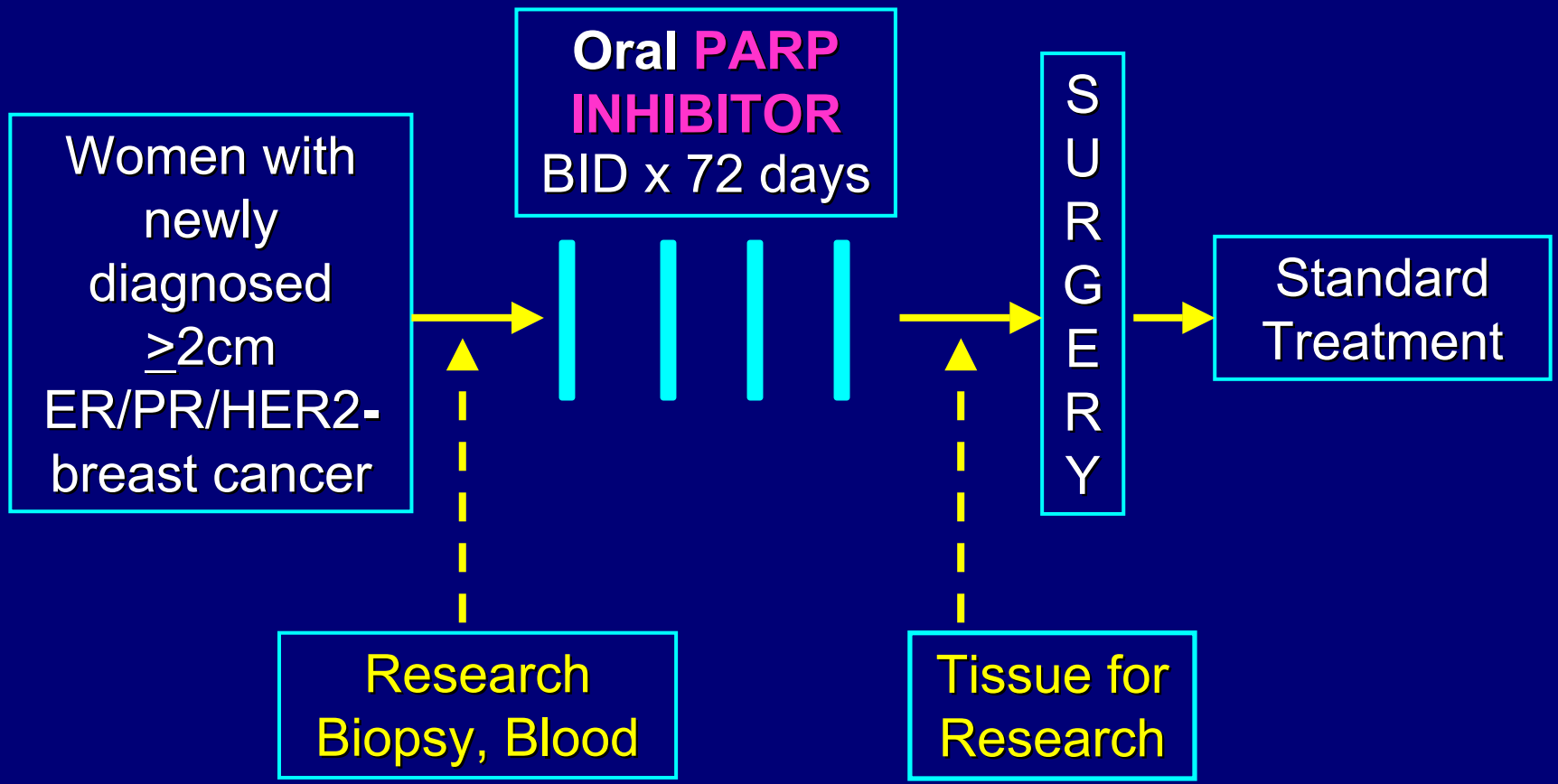
Produces large branched chains of poly(ADP-ribose)



A Tutt and A Ashworth

CDDP - Kudos PARP-Inhibitor trial in Triple Negative Breast Cancer

PI: J Garber, MD MPH, DFCI: DF/HCC, Val D'Hebron




"THE NEANDERTHAL BRAIN WAS LARGER THAN OURS. OUR BRAINS ARE GETTING SMALLER — SO WE BETTER GET IN ALL THE THINKING WE CAN AS SOON AS POSSIBLE