

PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

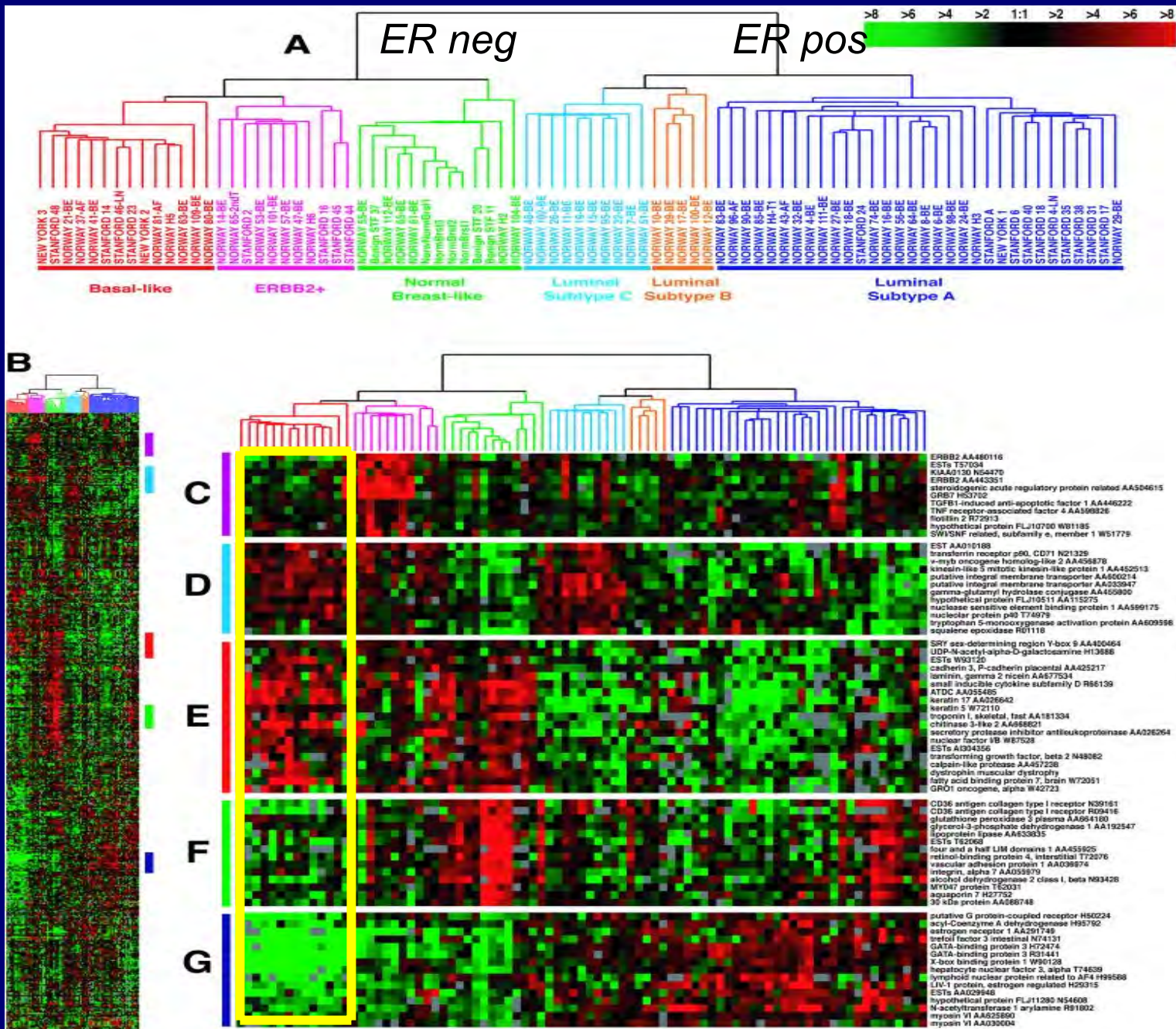
Preoperative Treatment of the Triple-Negative (Basal Phenotype) Breast Cancer

Judy E. Garber, MD MPH

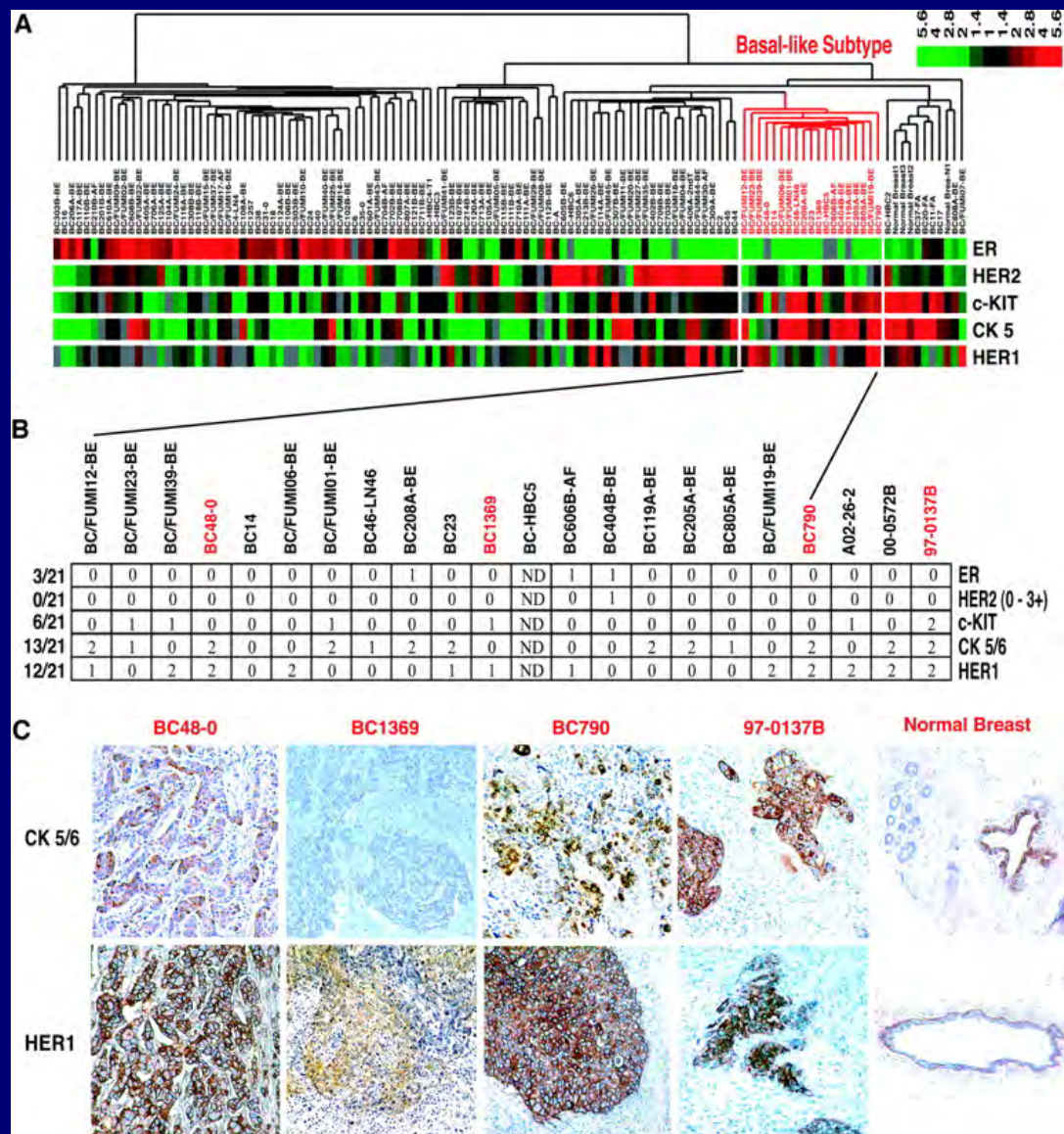
Dana Farber Cancer Institute

Boston, MA

26 March 2007



Gene Expression Profiles and IHC of Basal-like Breast Cancers



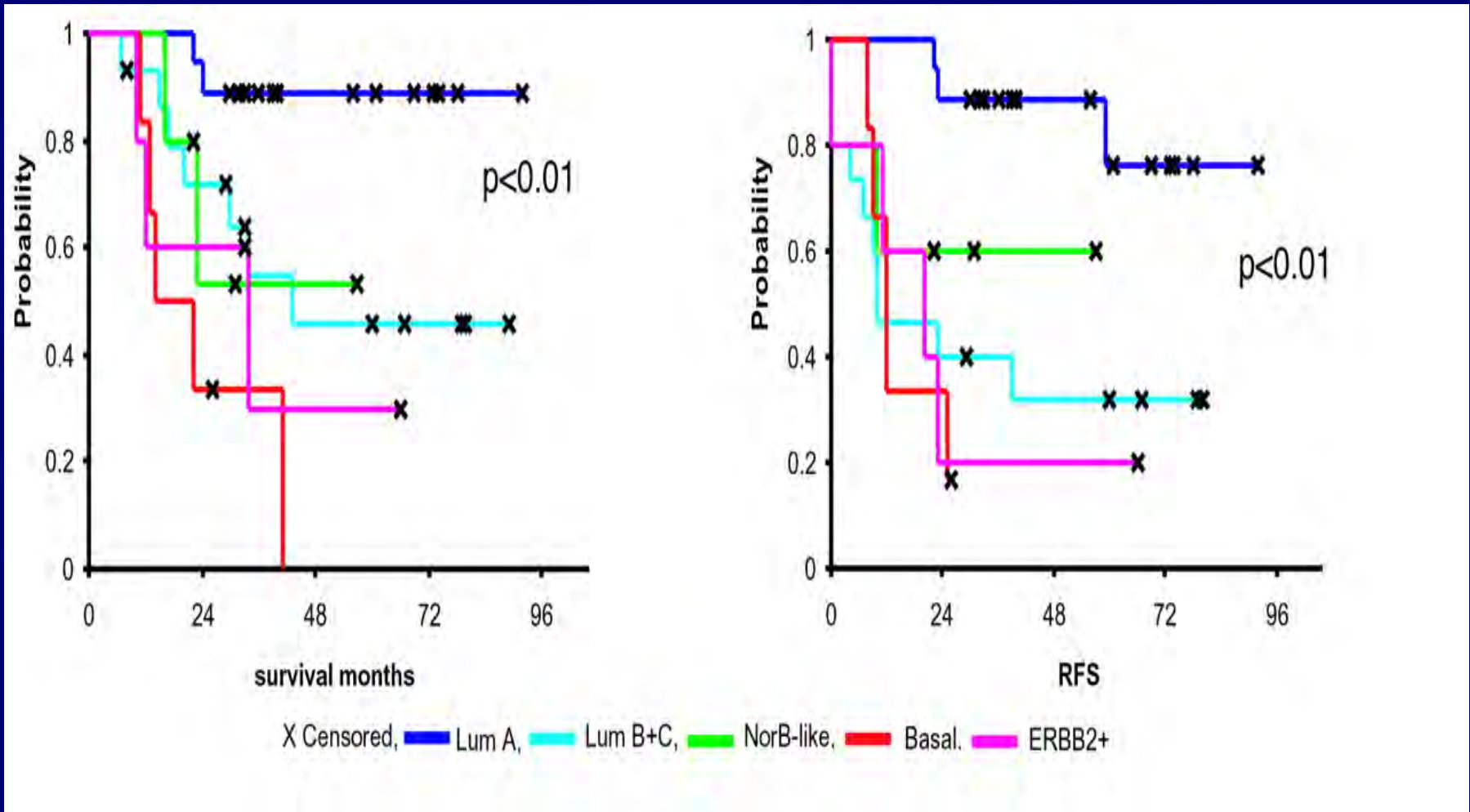
IHC Features of Basal-like v. Non-Basal-like Breast Cancers

	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

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)

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



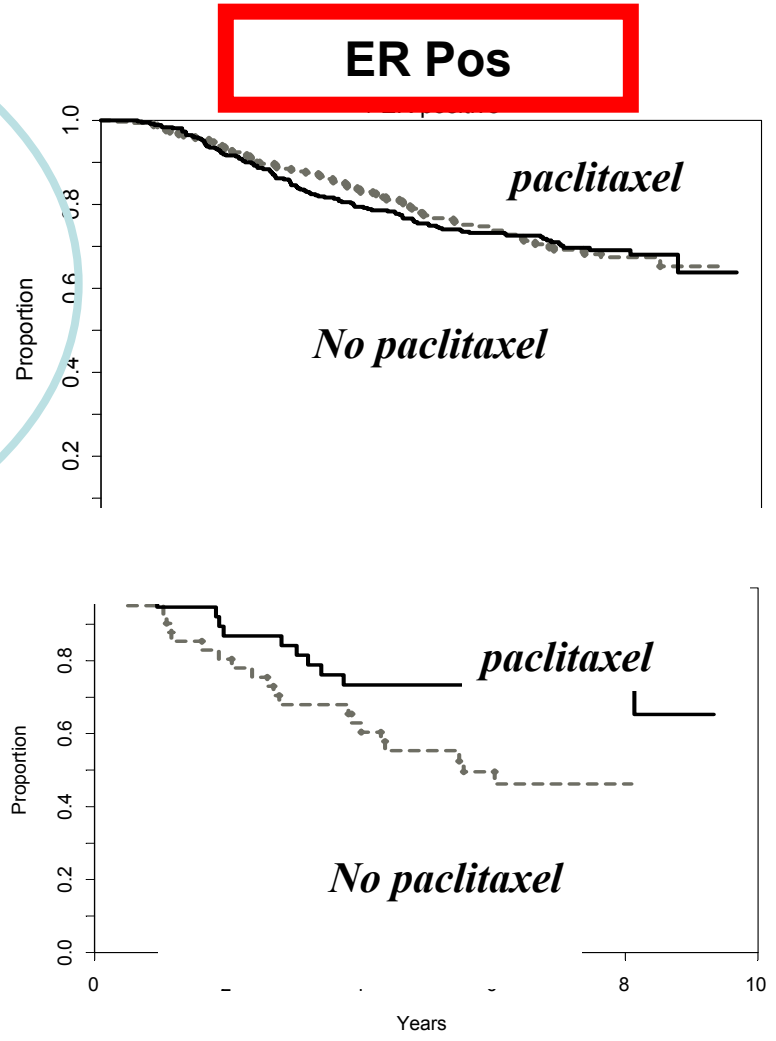
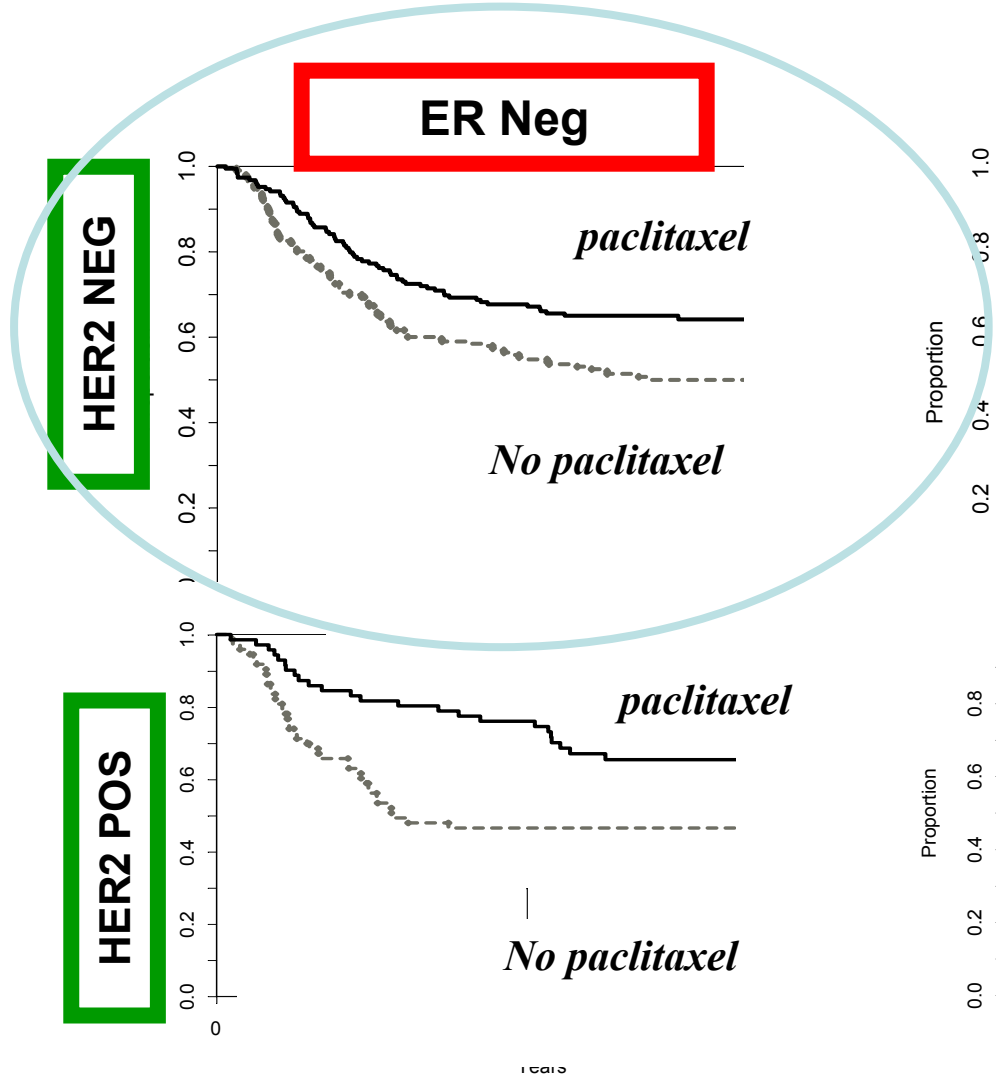
Correlation and Molecular Classification and Pathologic CR

<u>Subtype</u>	<u>T-FAC (n=82)</u>	<u>AC-T² (n=108)</u>
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%)

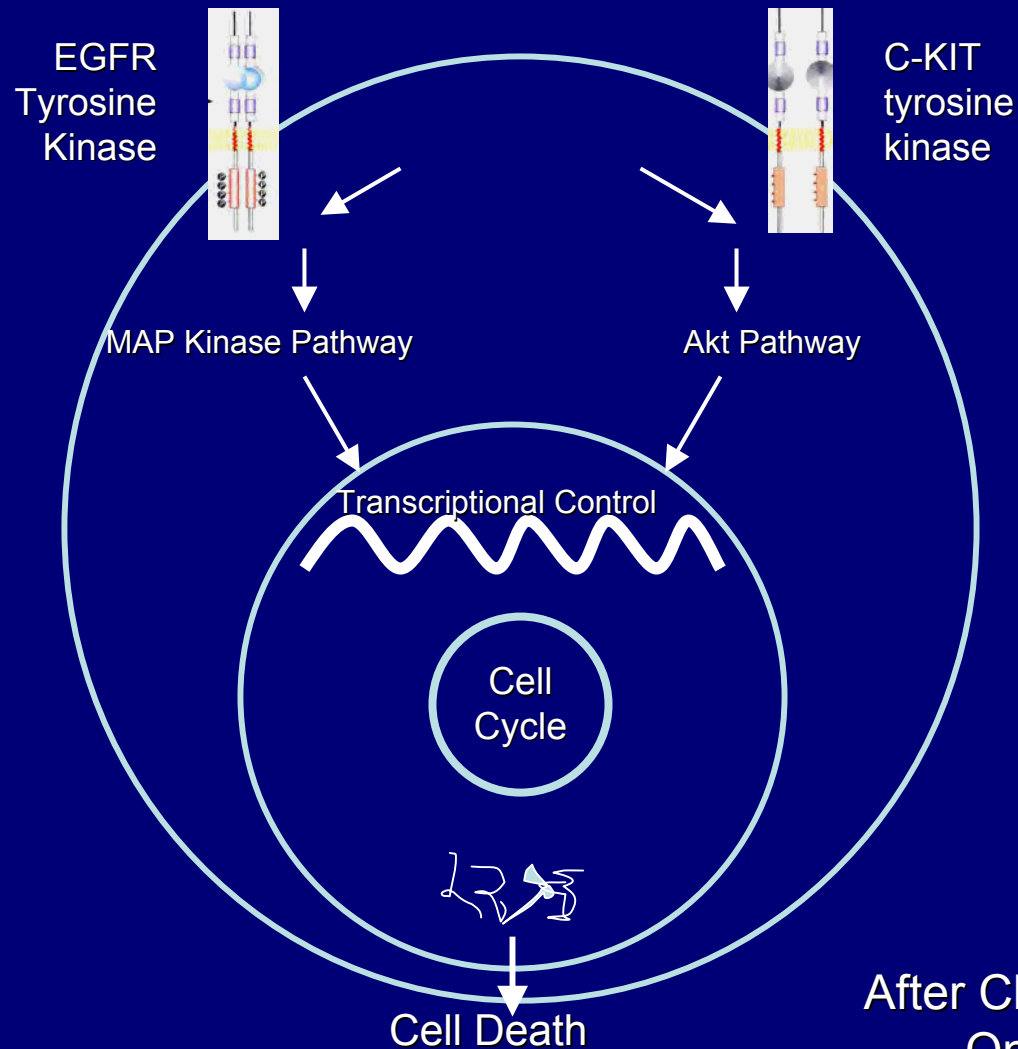
p<0.001

p=0.003

C9344 Disease-free Survival by ER and HER2

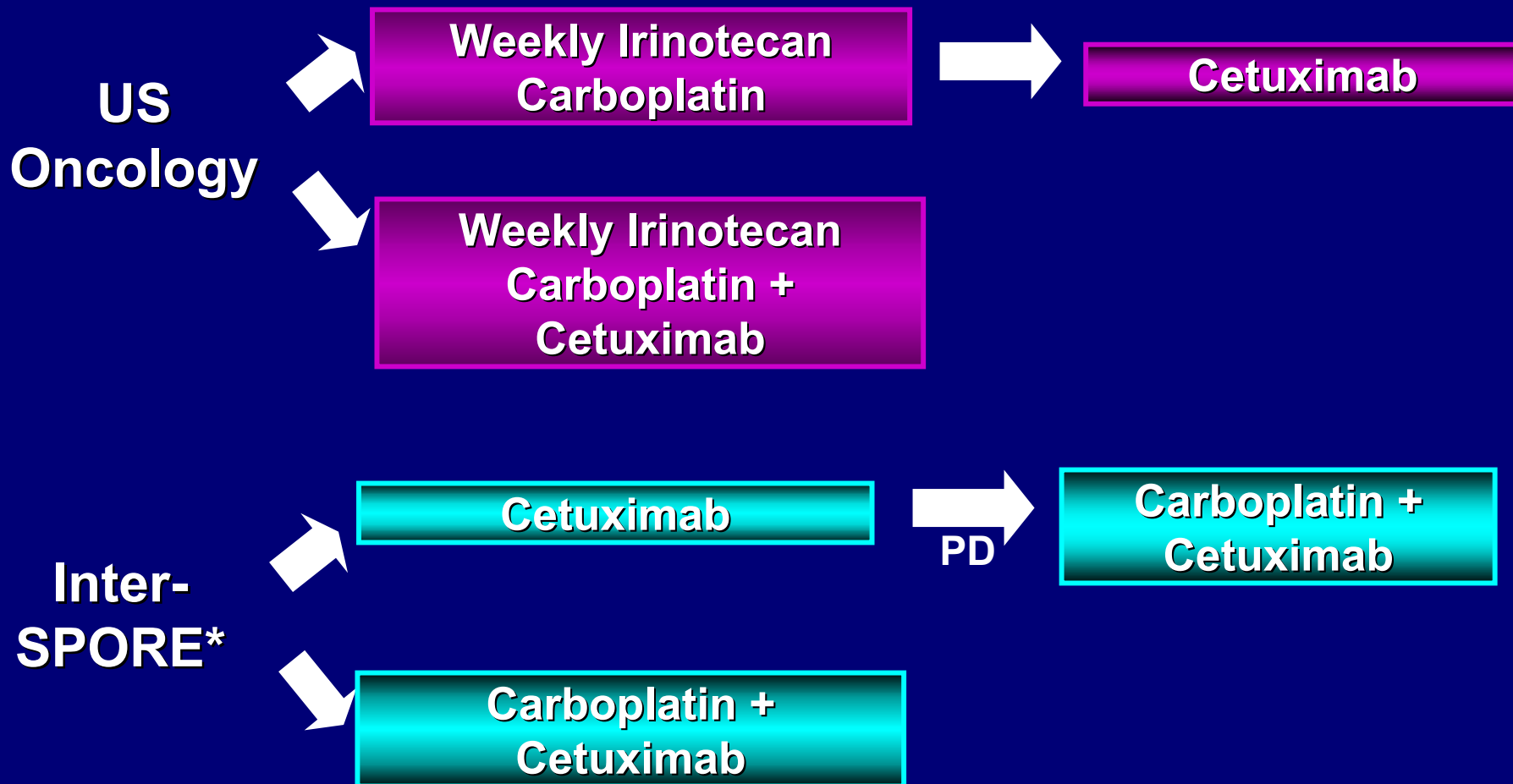


Triple-negative carcinoma: potential therapeutic targets



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

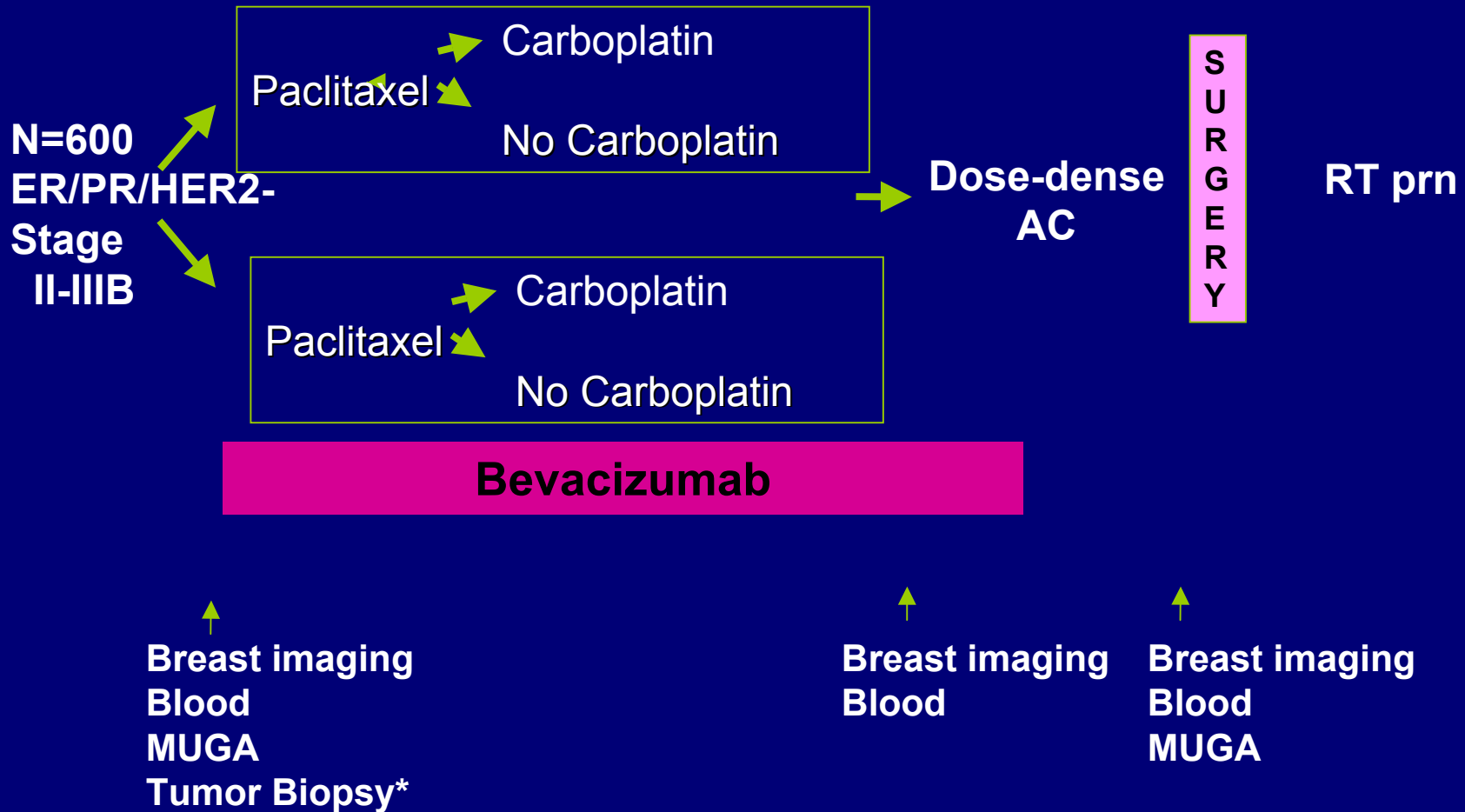
EGFR-Targeting Trials in Stg4 Triple Negatives



*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

ER/PR/HER2-
Stage
II-IIIB



Irinotecan q week/
UCN-01 day 1 of 21:
cycle is 42days

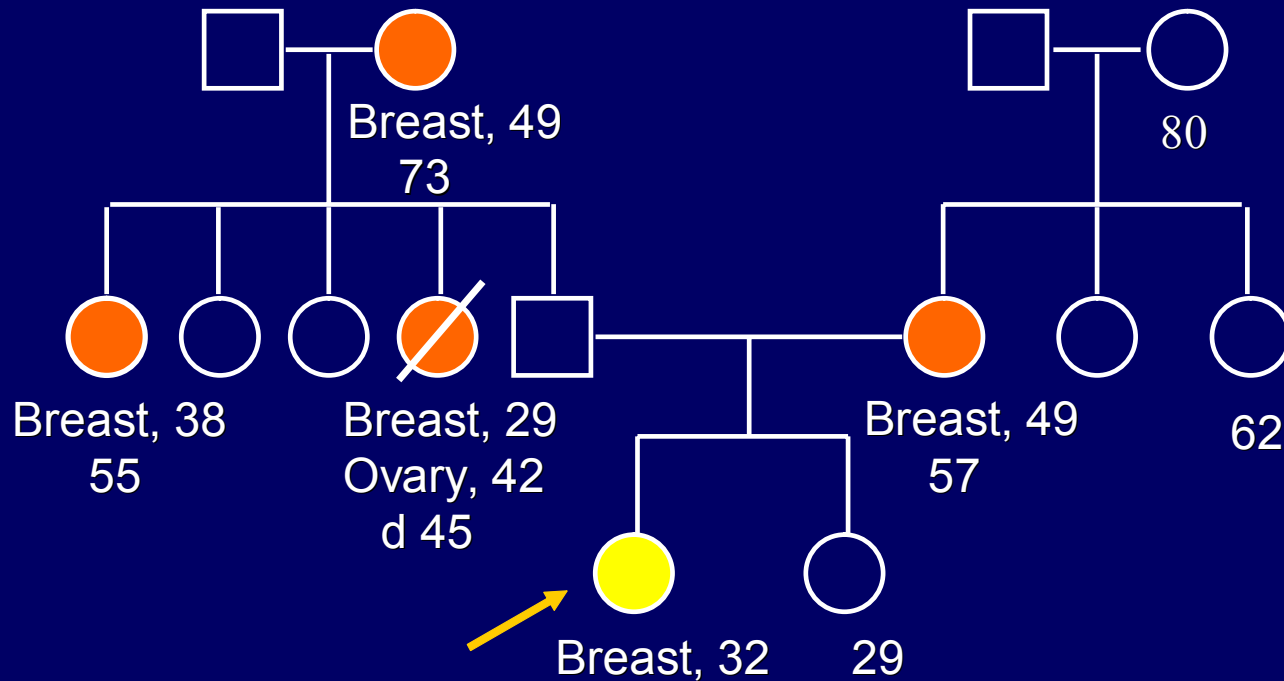


Unspecified

S
U
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Y

RT prn

A Classic Hereditary Breast/Ovarian Cancer Kindred



BRCA1 and BRCA2: Caretaker Genes

Maintenance of genomic integrity through:

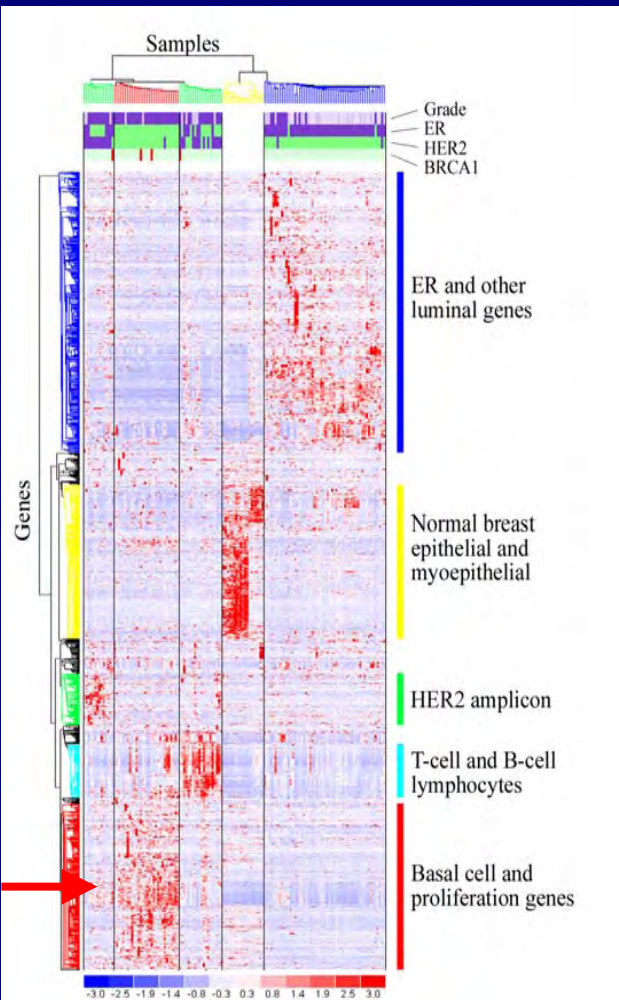
- DNA damage recognition and repair
- Transcriptional regulation of gene expression
- Chromatin remodeling
- Cell cycle checkpoint control

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

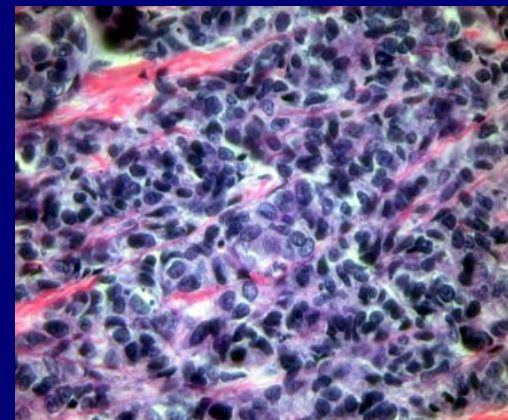
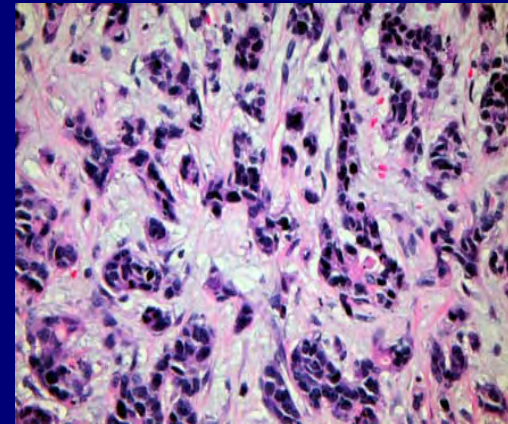
Class	N (%)	ER+%	p ^a
<u>BRCA1</u>			
Age <45	59 (24.7)	19.0	
Age 45-55	72 (30.1)	31.1	
Age 55-65	108 (45.2)	38.0	p=0.020
<u>BRCA2</u>			
Age <45	43 (48.8)	83.7	
Age 45-55	35 (39.8)	71.4	
Age 55-65	10 (11.4)	80.0	p=0.418

BASAL-LIKE BREAST CANCERS

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

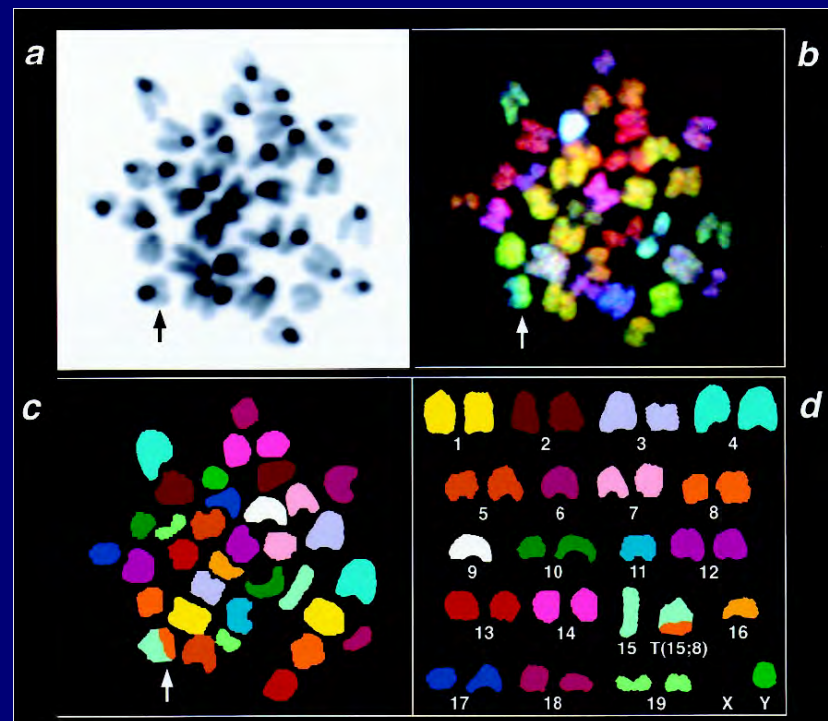
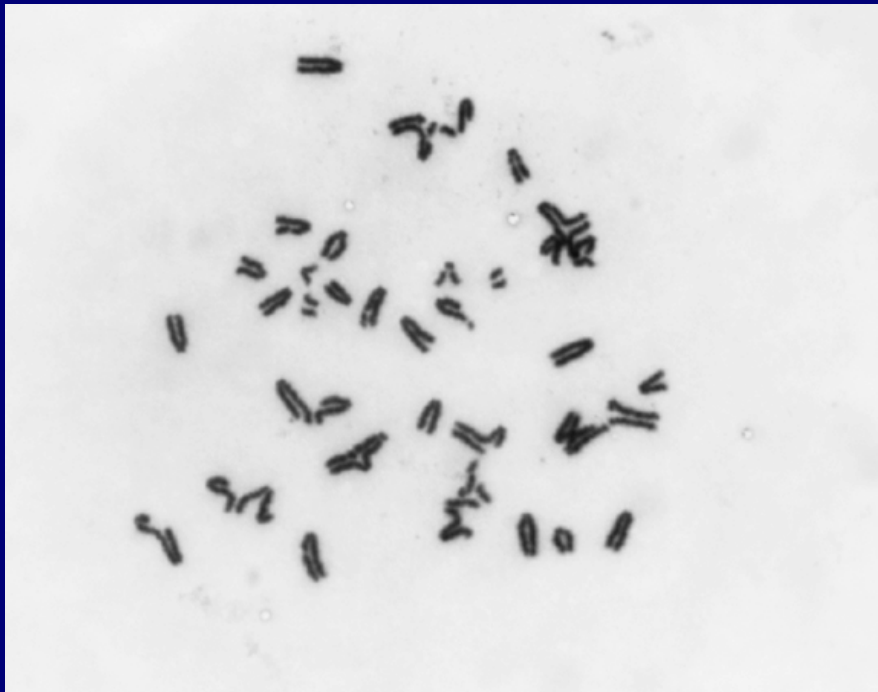


- 10% of breast cancers
- ER(-) PR(-) HER2(-)
- Poorly differentiated
- High grade, Aneuploid
- EGFR+, cyclin E+
- Express basal keratins CK5/6; Vimentin
- Little DCIS
- Poor prognosis
- Different stem cell?

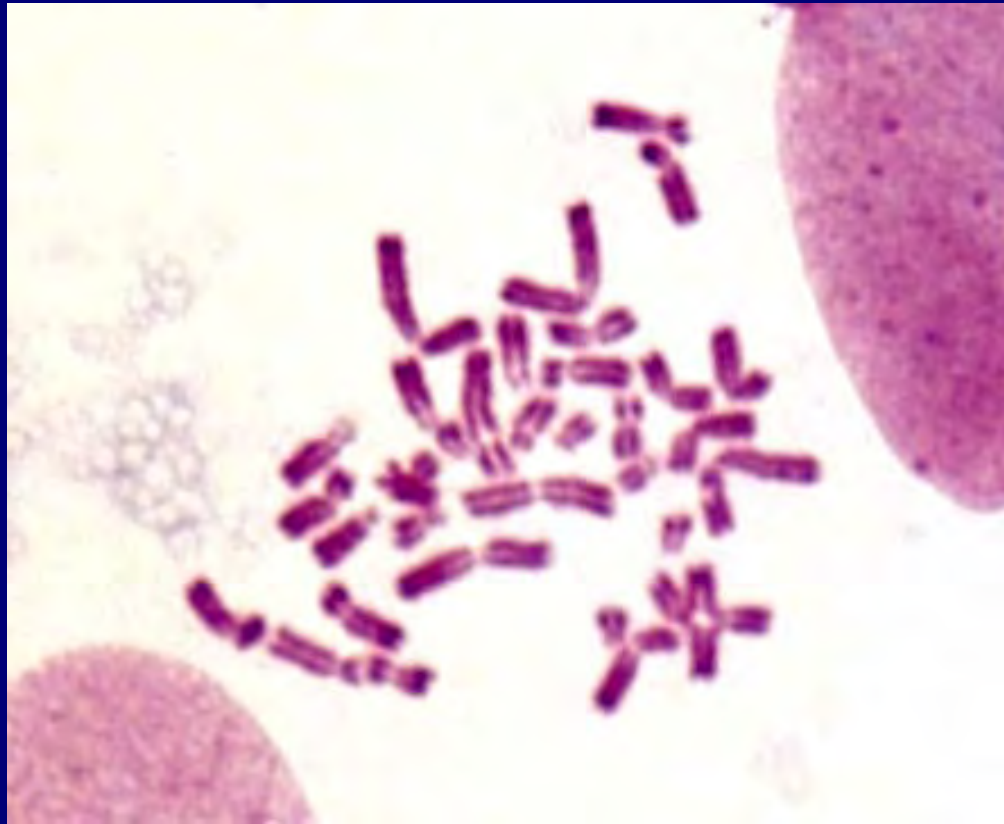


BRCA1-deficient cells develop gross chromosomal abnormalities with DNA damage

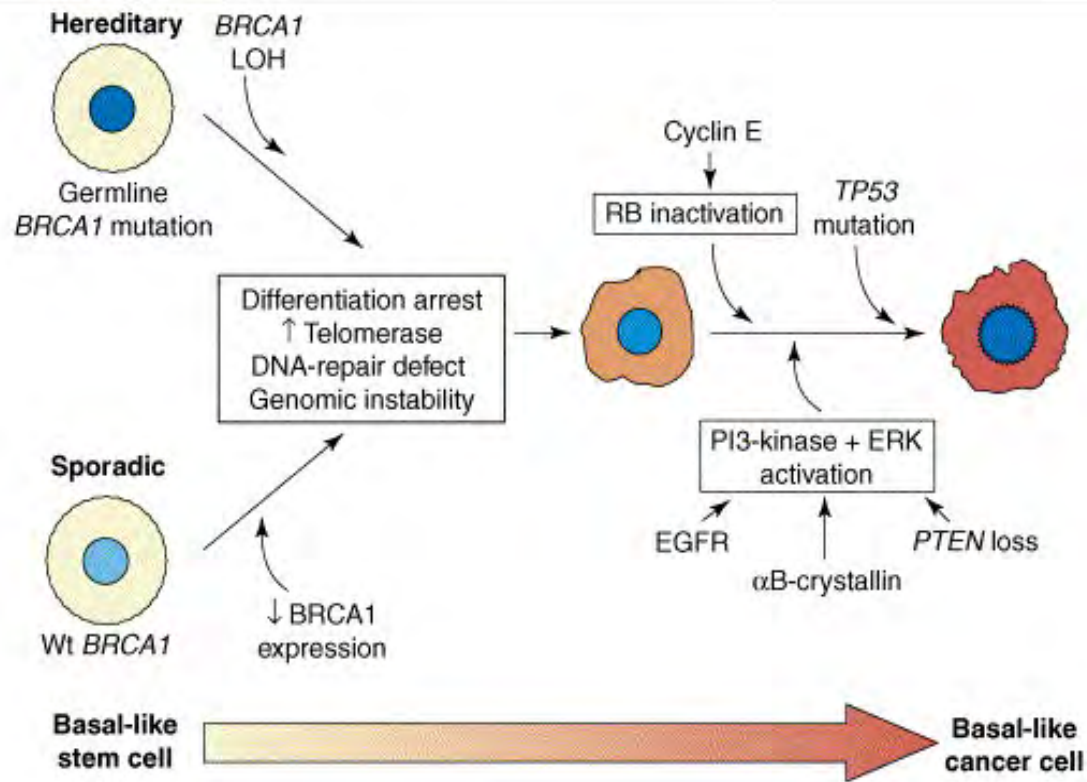
	Total # of metaphases	% Abnormal	# of Embryos
Brcal ^{+/+} or Brcal ^{+/-}	97	3.1	4
Brcal ^{-/-}	47	31.9	6
Brcal ^{+/-} p53 ^{+/-}	41	2.4	1
Brcal ^{+/-} p53 ^{-/-}	38	2.6	1
Brcal ^{-/-} p53 ^{-/-}	76	72.4	2



Basal-like Tumors Show DNA Damage Sensitivity



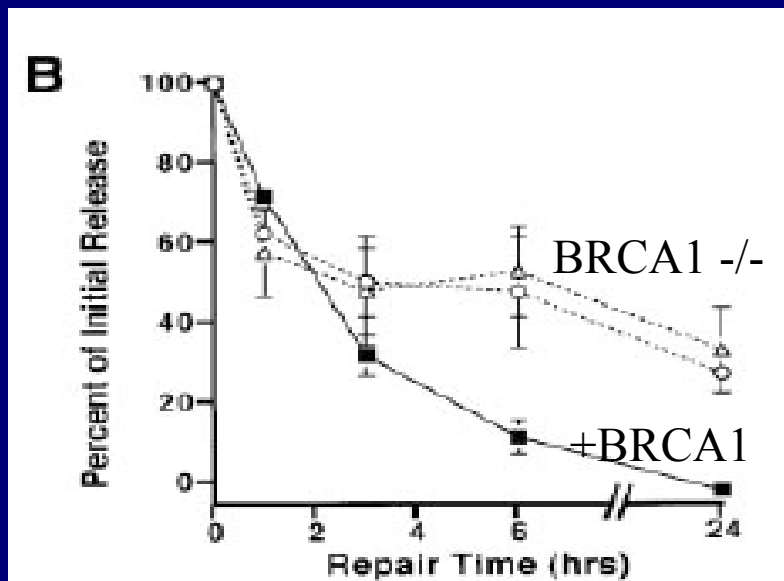
Working Model for BRCA1- and Sporadic Breast Cancer Pathogenesis



TRENDS in Molecular Medicine

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

γ -Radiation



Scully, Ganesan et al, Mol. Cell 1999

Mitomycin C

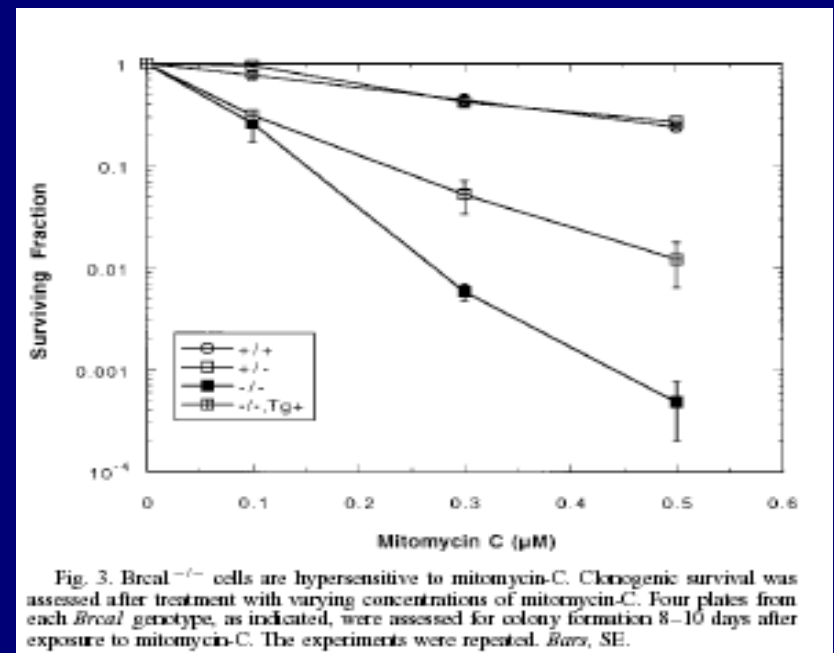
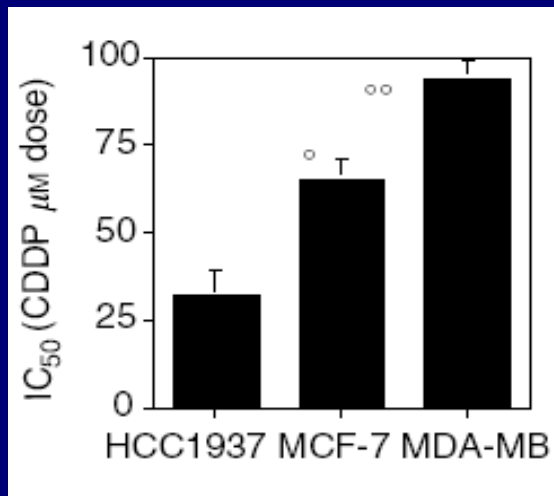


Fig. 3. *Brca1*^{-/-} cells are hypersensitive to mitomycin-C. Clonogenic survival was assessed after treatment with varying concentrations of mitomycin-C. Four plates from each *Brca1* genotype, as indicated, were assessed for colony formation 8–10 days after exposure to mitomycin-C. The experiments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

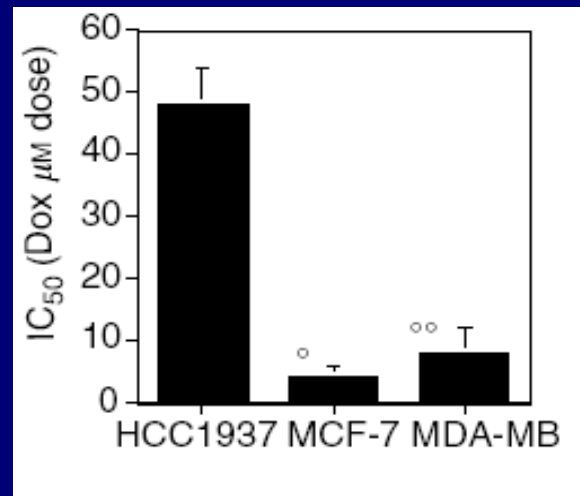
Moynahan et al, Cancer Res 2001

BRCA1-Deficient Cells Are Hypersensitive to Cisplatin

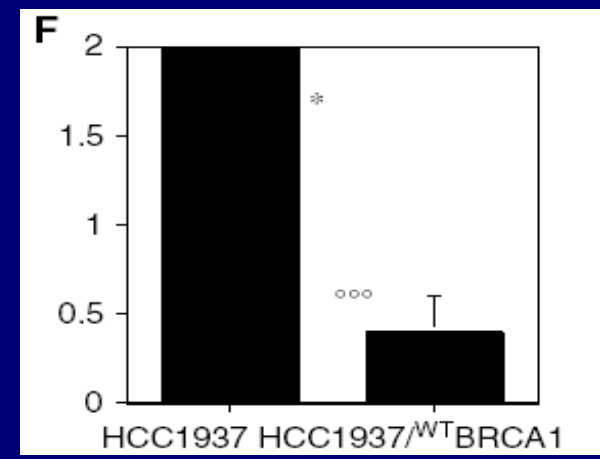
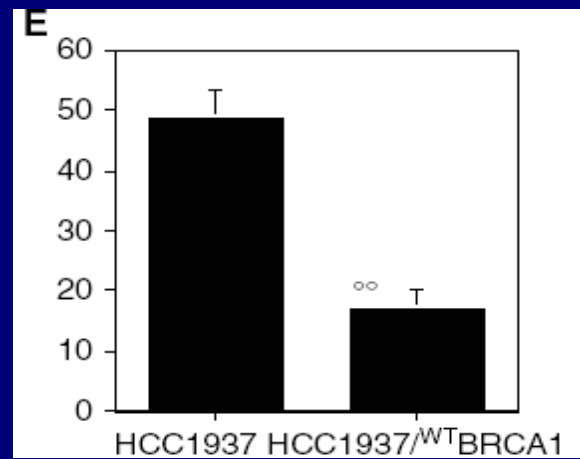
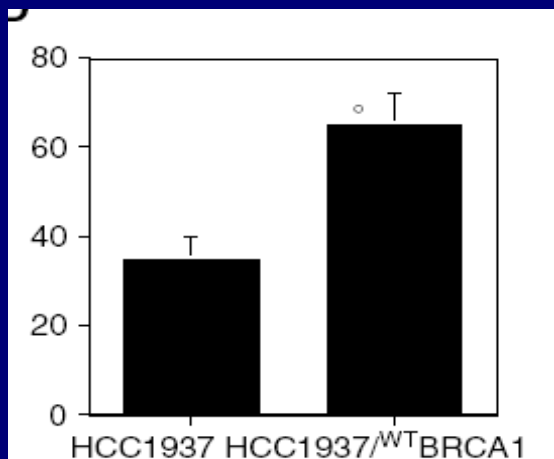
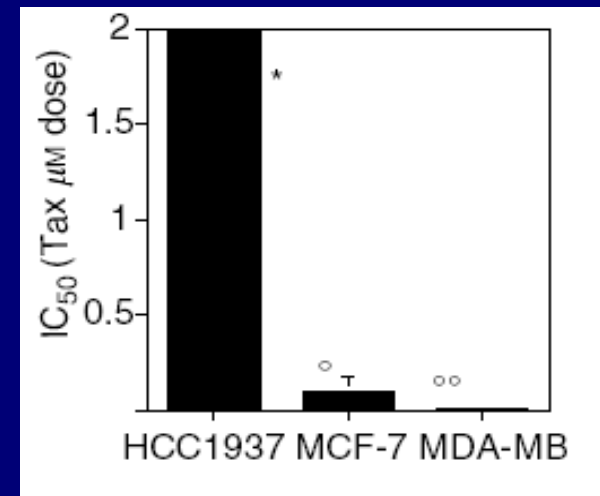
CISPLATIN



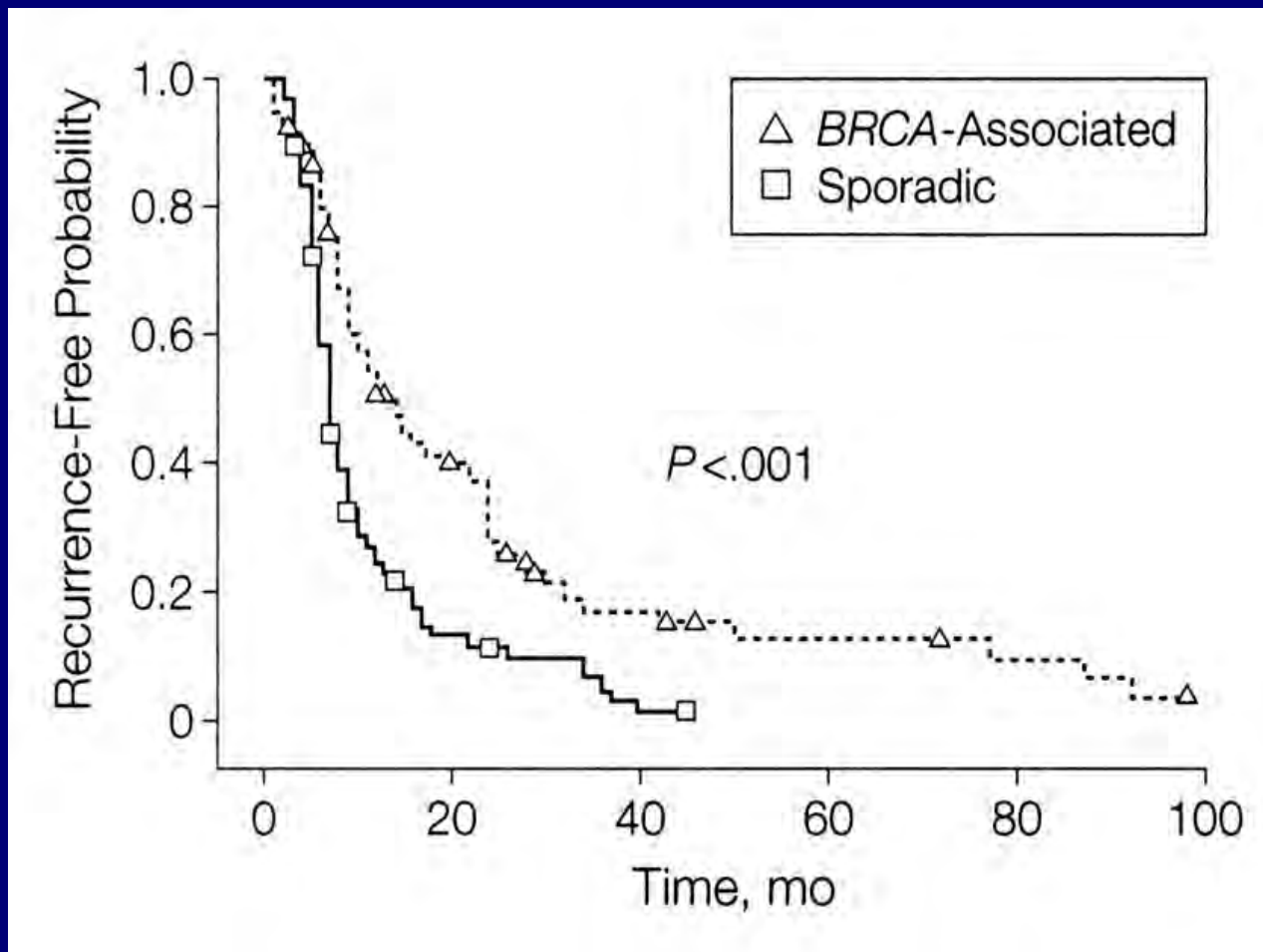
DOXORUBICIN



PACLITAXEL



Recurrence-Free Interval Probabilities in Patients with Advanced Ovarian Cancers



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

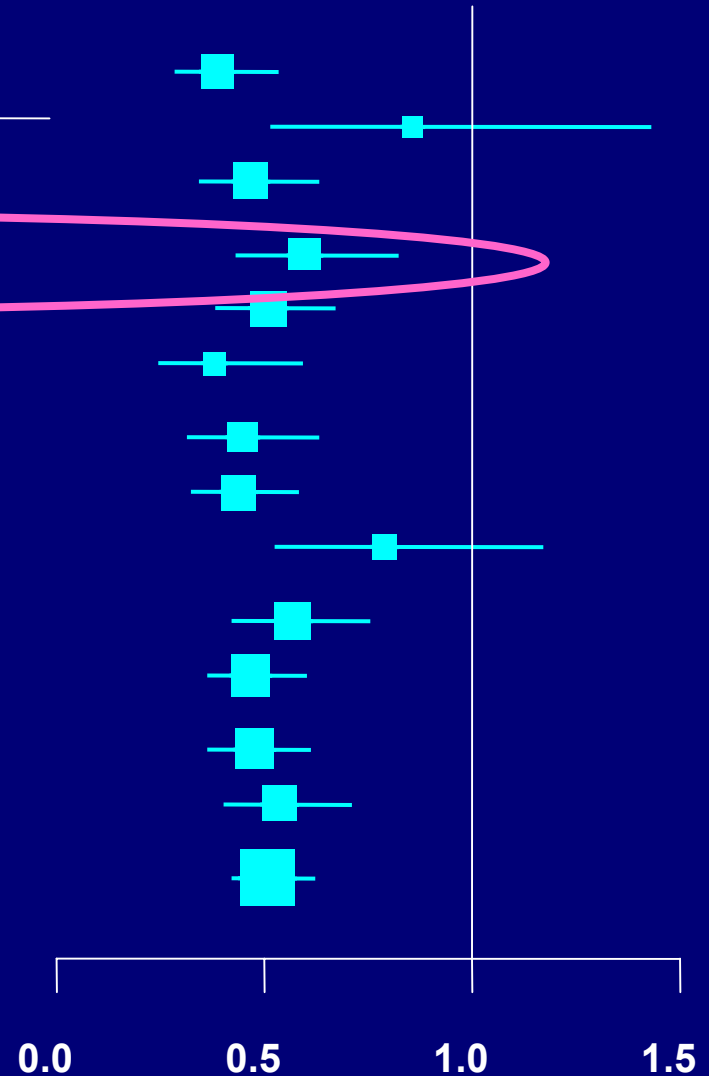
Responses to Neo-Adjuvant CDDP (n=28)

<u>Response</u>	<u>Clinical</u>	<u>Pathologic</u>
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

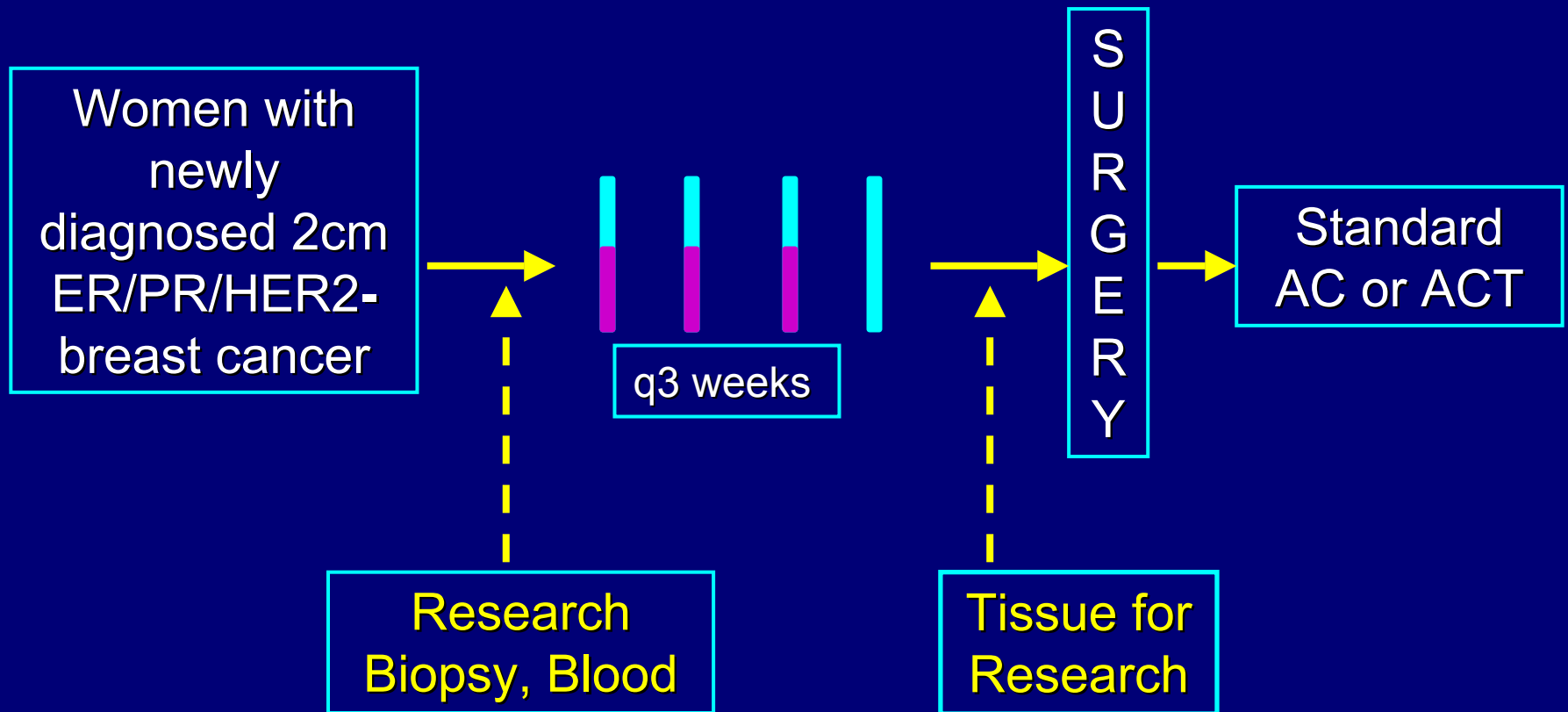
Bevacizumab in Clinical Subsets

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



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

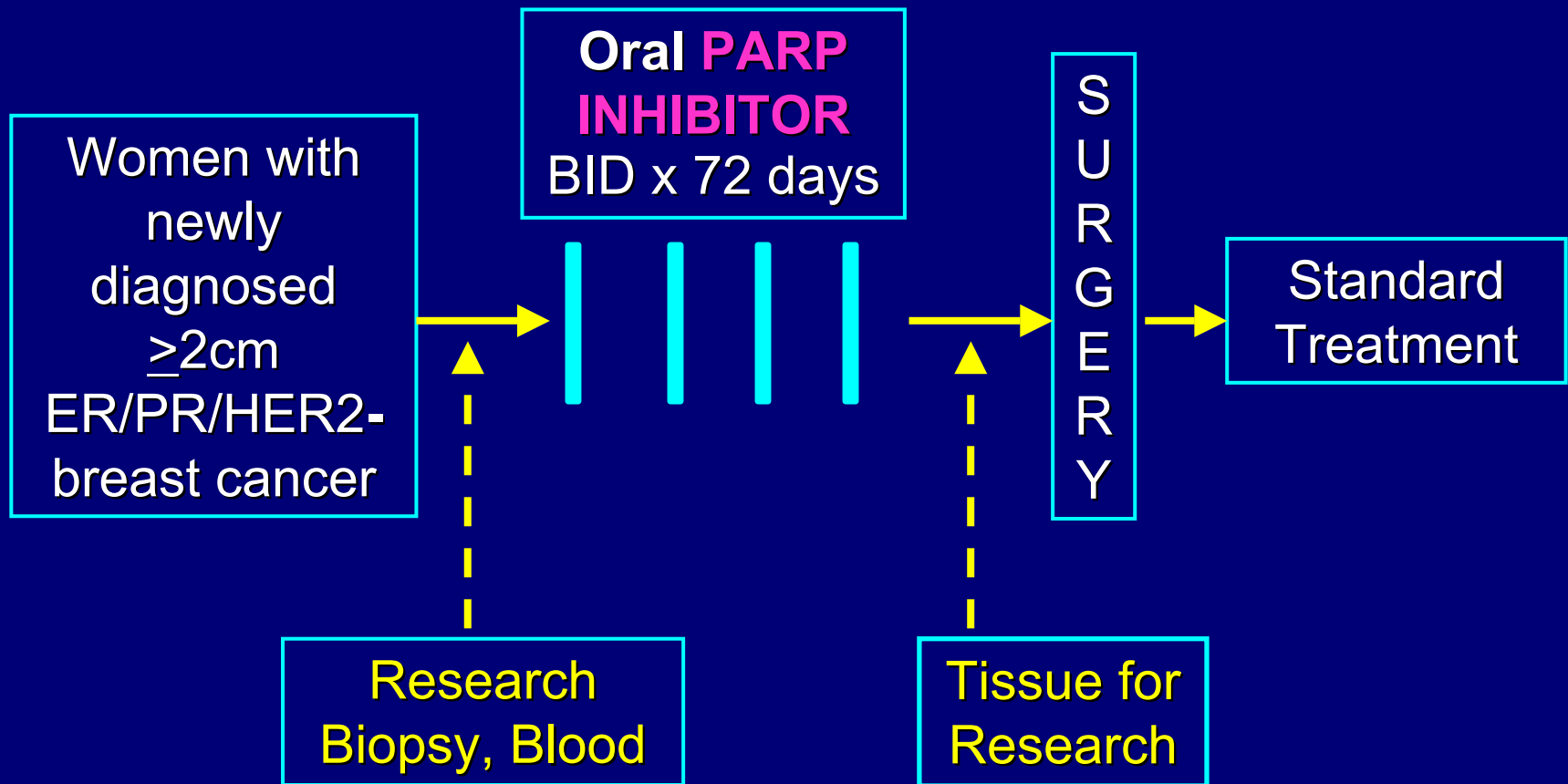
Binds directly to DNA damage

Produces large branched chains of poly(ADP-ribose)



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