The elements & clinical care of triple-negative breast cancer

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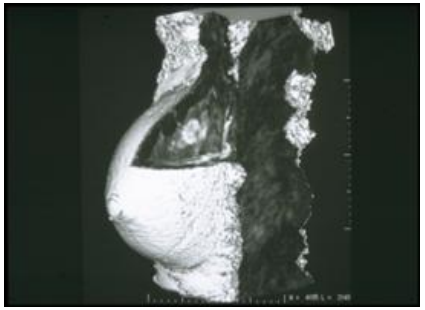
Outline

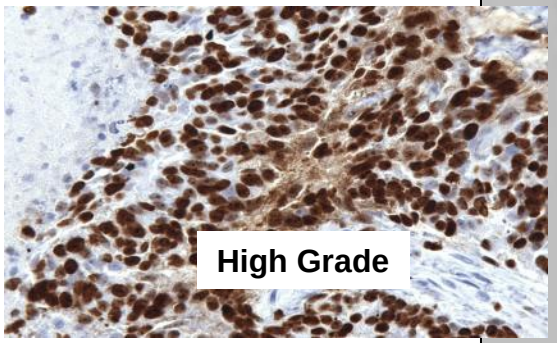
- **Clinical features of triple-negative breast cancer**
- **Treatment implications of germline BRCA1 & BRCA2 mutations in TNBC**
- **Update on platinum in BRCA+ and sporadic TNBC**
- **Emerging concepts in immunotherapy**

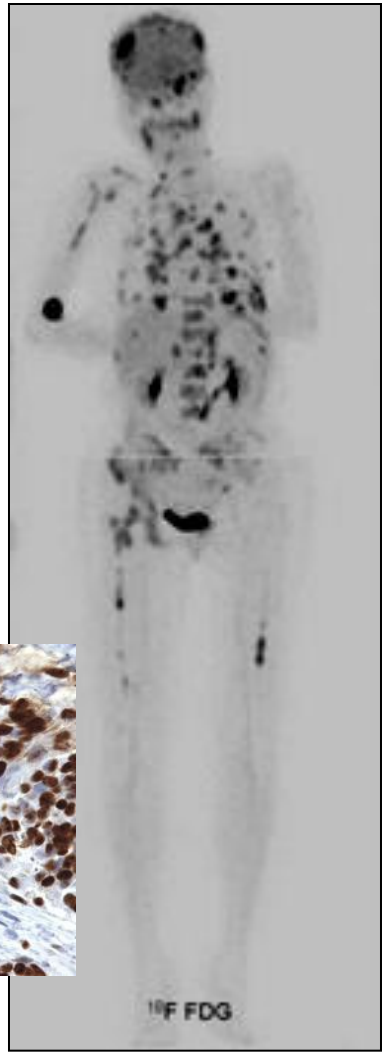
Triple-Negative Breast Cancer

Current Status

- **Standard treatment for early-stage TNBC in 2014 consists of combination chemotherapy**
  - Anthracycline and taxane-based
  - Has not changed significantly in 10++ years
- **Selective use and targeting of available cytotoxics not optimized**
  - Starting to see changes here!
- **Germline BRCA1/2 status generally not reported in trials**
  - Important to truly understand results in this disease







Triple-Negative Breast Cancer

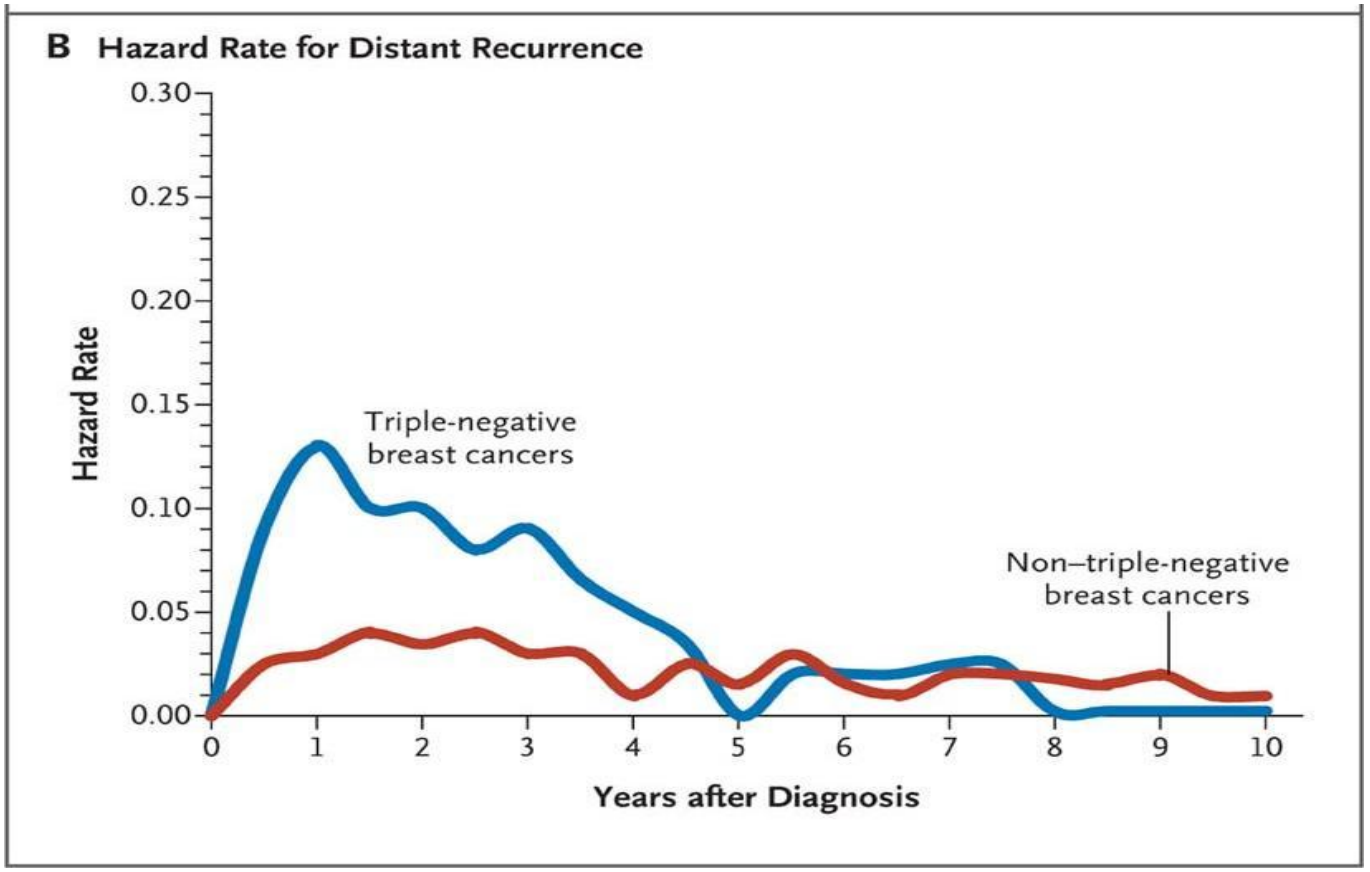
- **13% of all breast cancer in California**
  - California Cancer Registry 1999-2005; n=87,604

- **Varies by ethnicity/race**
  - White: 11%
  - Japanese 11%
  - Chinese 11%
  - Black: 26%
  - Hispanic: 17%

- **Disproportionately affects the young (<40)**

Telli ML, et al. Breast Cancer Res Treat, 2011

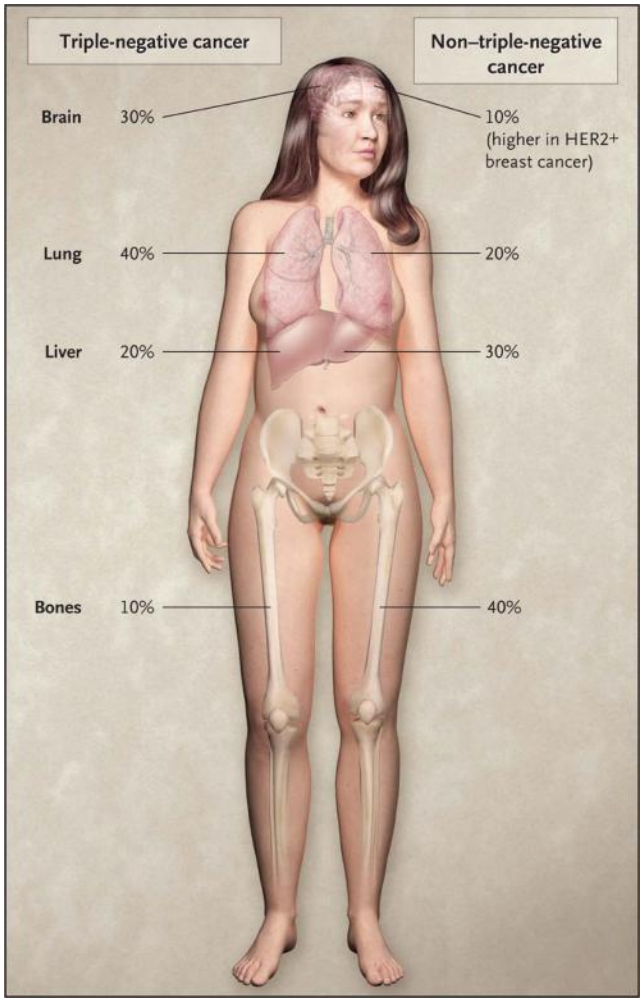
Early risk of recurrence



Foulkes WD et al. N Engl J Med 2010;363:1938-1948

The NEW ENGLAND JOURNAL of MEDICINE

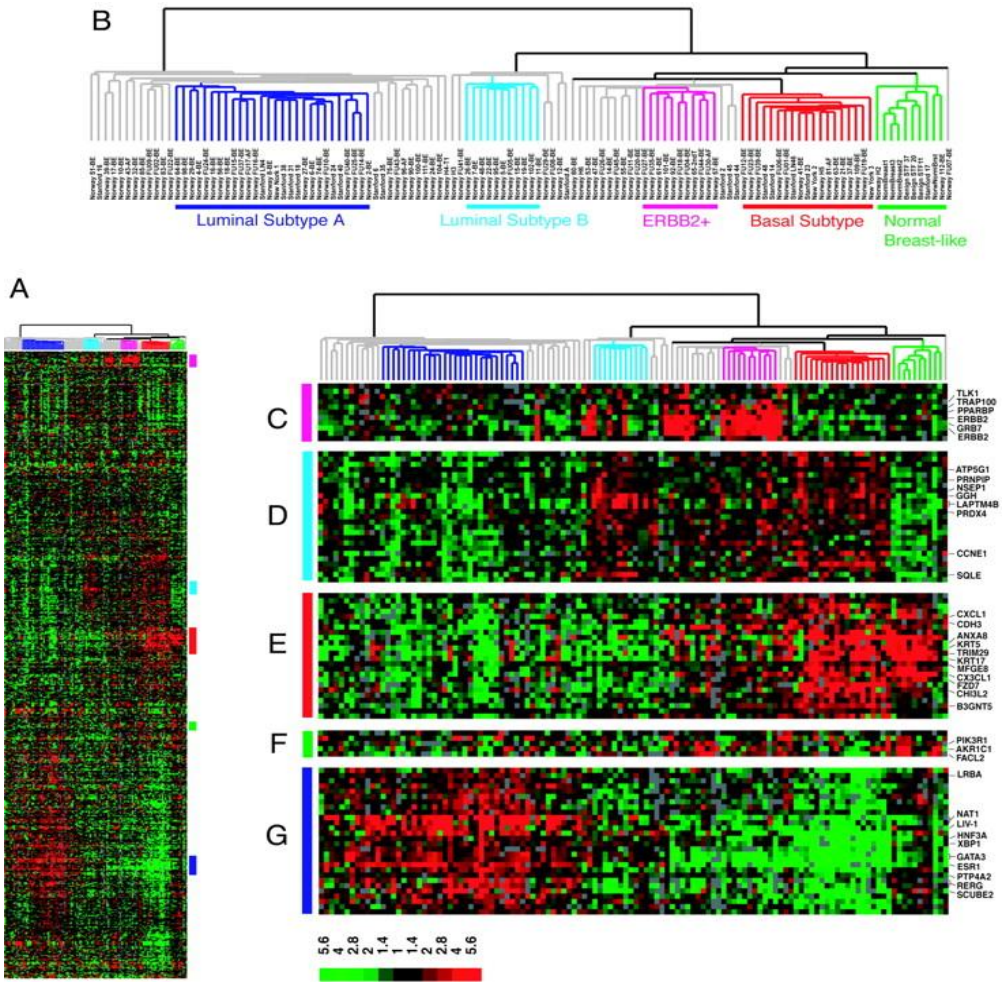
Sites of First Distant Recurrence



Foulkes WD et al. N Engl J Med 2010

The NEW ENGLAND JOURNAL of MEDICINE

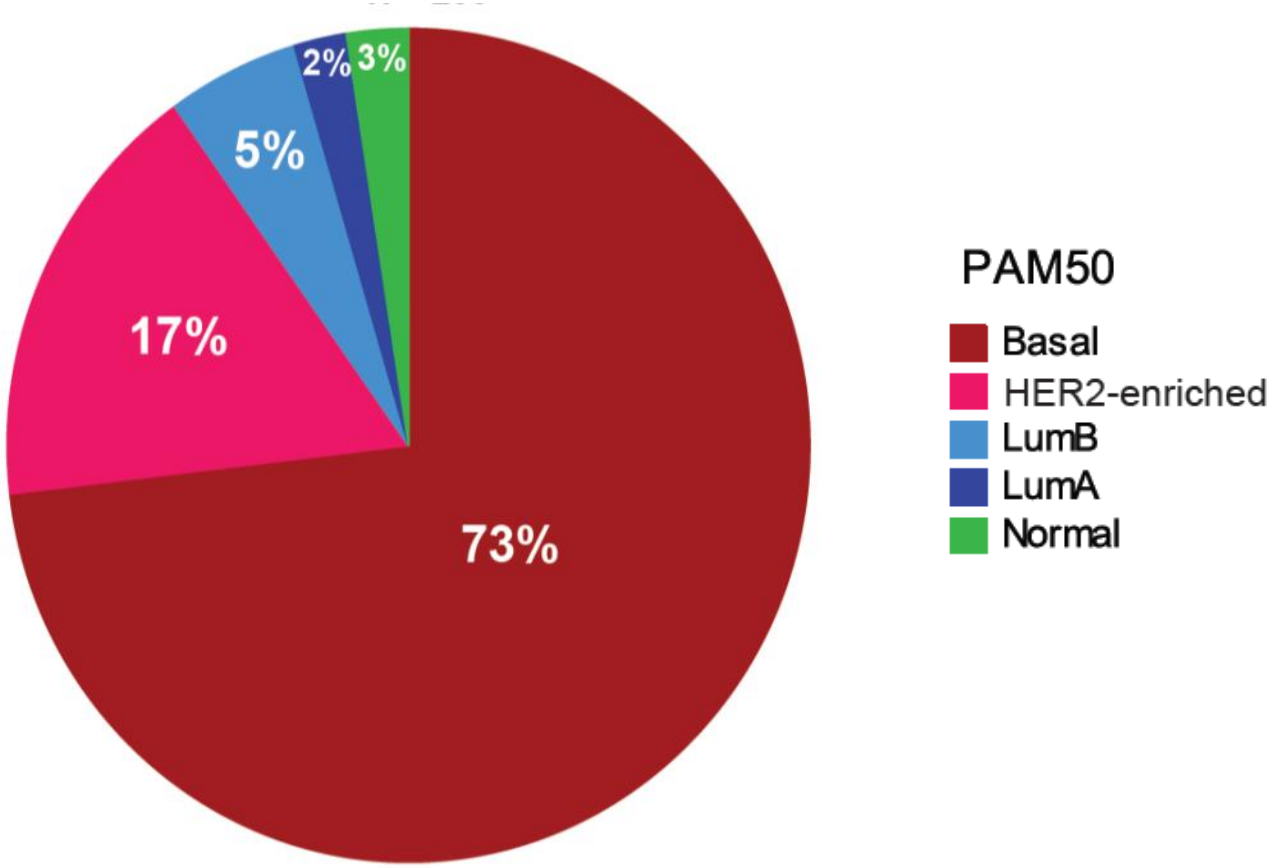
Breast Cancer Intrinsic Subtypes



Most triple-negative breast cancers are 'basal-like' by gene expression

Sørlie T et al. PNAS 2003;100:8418-8423

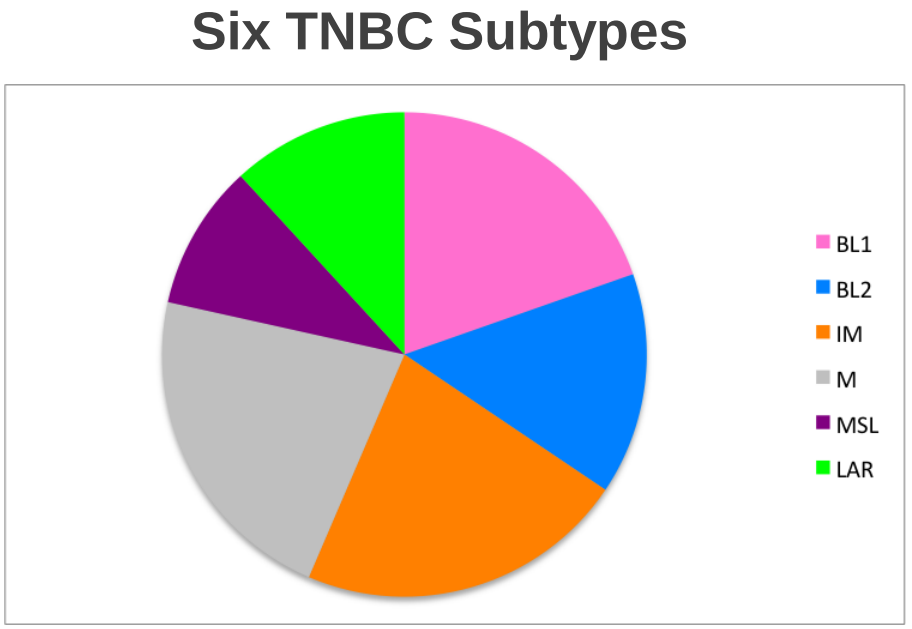
Intrinsic Subtype Distribution Among Clinically Triple-Negative Breast Cancers



Cheang M, et al. ASCO 2012

Vanderbilt TNBC Subtypes

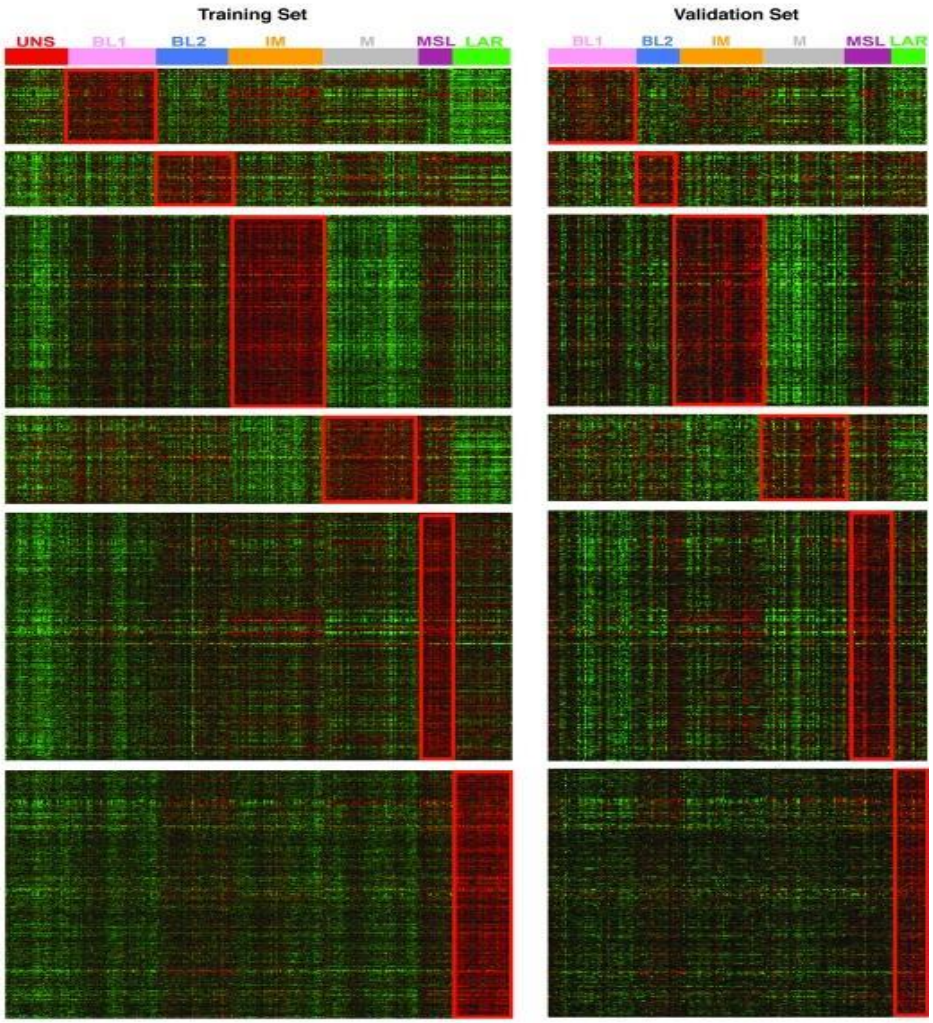
- Analyzed gene expression profiles from 21 breast cancer data sets (587 cases of TNBC filtered by ER, PR, HER2 mRNA expression)
- Identified 6 TNBC subtypes by cluster analysis displaying unique gene expression and ontologies



Adapted from Lehmann et al; excludes 62 unclassified cases

Lehmann BD, et al. Journal of Clinical Investigation, 2011

Vanderbilt TNBC Subtypes



Basal-like 1 (BL1): Cell-cycle, proliferation and DNA damage response genes

Basal-like 2 (BL2): Growth factor signaling (EGF, MET, Wnt/β-catenin, IGF1R)

Immunomodulatory (IM): Immune cell and cytokine signaling (overlap with medullary breast cancer gene signature)

Mesenchymal (M): Cell motility and differentiation (Wnt, ALK, TGF-β)

Mesenchymal stem-like (MSL): Similar to M, but increased growth factors signaling, low proliferation, enrichment of genes associated with stem cells

Luminal androgen receptor (LAR): Enriched in hormonally-regulated pathways, androgen receptor signaling. Displays luminal expression patterns (molecular apocrine carcinomas)

Lehmann BD, et al. Journal of Clinical Investigation, 2011

Targeting the androgen receptor (AR) in women with AR+ ER-/PR- metastatic breast cancer

ER/PR(-) (IHC ≤10%) LABC/MBC

Measurable/ non-measurable
No limit to prior therapy

→ **AR testing**

Central testing at MSKCC*

→ **AR(+)**

IHC >10%

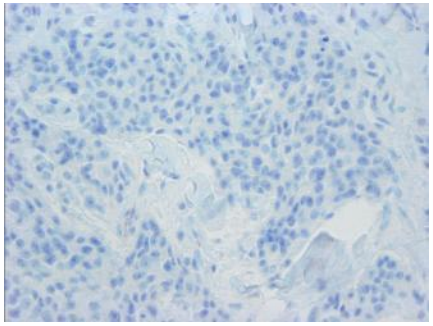
12% AR+

→ **Bicalutamide 150mg daily**

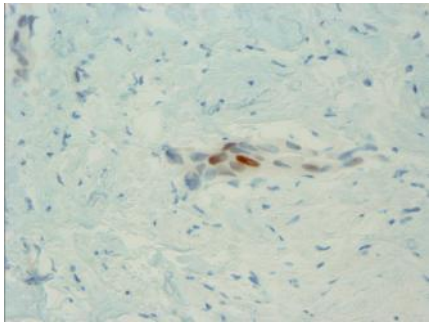
1 cycle = 4 weeks

Toxicity evaluation every 4 weeks (± 5 days)
Response evaluation by RECIST every 12 weeks (± 2 weeks)

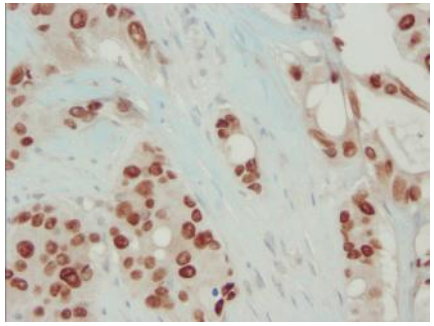
***AR tested using primary antibody AR 441 (Dako; dilution: 1:300)**



0%



11-15%



100%

Gucalp A, et al., Clin Cancer Research 2013

Results: Patients with Clinical Benefit (5/24 = 21%)

Patients with clinical benefit on bicalutamide	AR%	ER%	PR%	HER2	Site of Testing	Site of Mets	Prior Therapy MBC/ LABC	DOR on Prior Therapy
#1	10-20	1	0	Neg	1^0	LN	0	NA
#2	>80	3	0	Neg	Met	GI	0	NA
#3	>80	0	0	-/+	1^0	Breast, LN	1	NR
#4	>90	0	0	Neg	1^0	LN, Bone	1	158wk
#5	>50	0	0	Neg	1^0	LN, Bone	1	15 wk

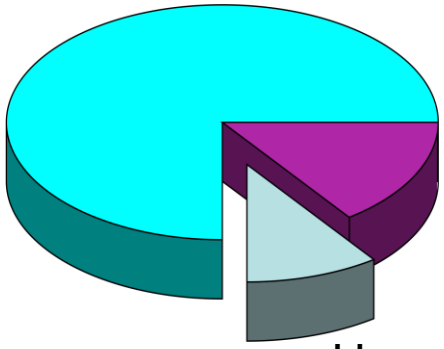
Gucalp A, et al., Clin Cancer Research 2013

The search for a target:

Clues from cancer genetics

Hereditary Breast and Ovarian Cancer

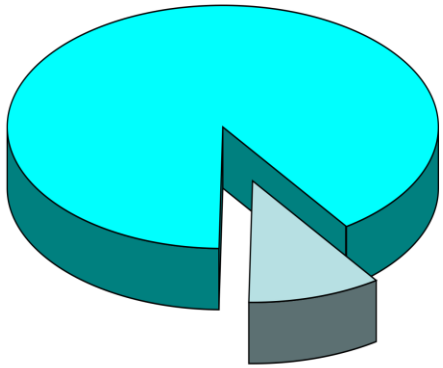
Breast



Family clusters: 15-20%

Hereditary: 5-10%

Ovarian



Hereditary: 10-15%

- Most hereditary breast and ovarian cancers are due to germline BRCA1 and BRCA2 mutations

- BRCA1/2-associated cancers are compromised in **DNA repair**

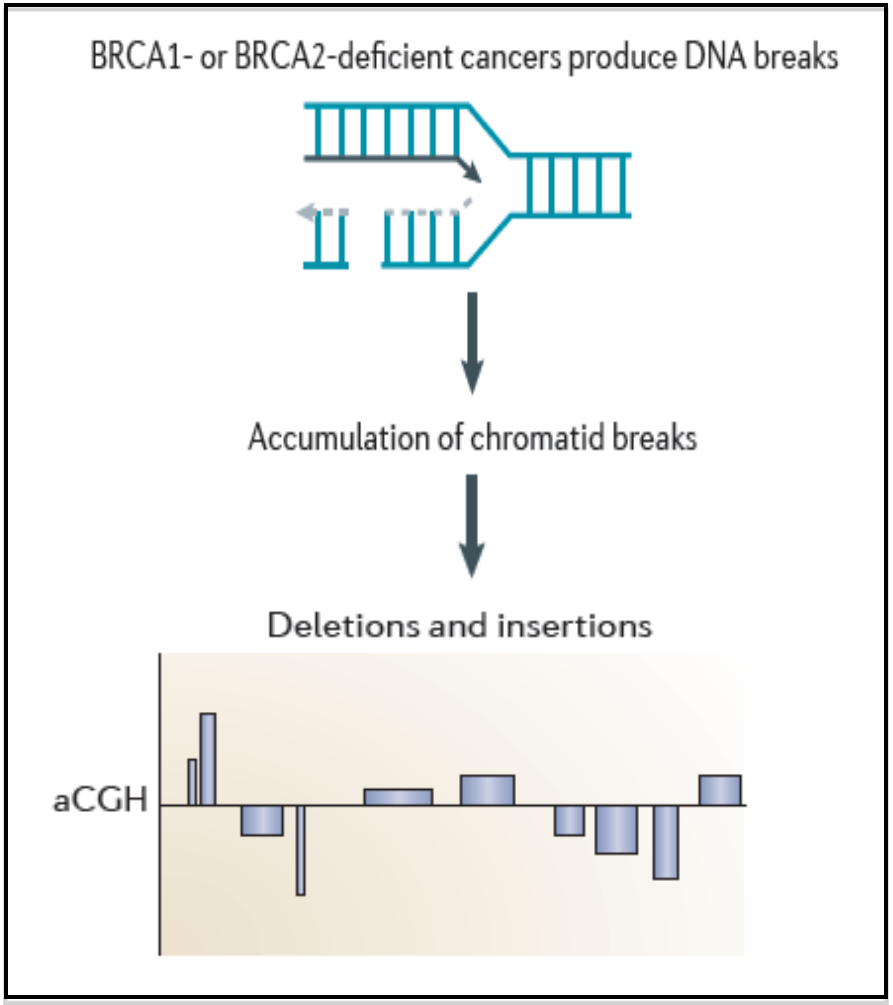
Association between TNBC & germline mutations in BRCA1/2

- **Approximately 75-80% of BRCA1 mutation-associated breast cancers are basal-like by gene expression or IHC** [1,2]

- **In unselected TNBC, frequency of BRCA1/2 mutations reported to be up to 19.5%**[3]

1. Sorlie, et al. PNAS, 2003
2. Foulkes WD, et al. Cancer Research, 2004
3. Gonzalez-Angulo AM, et al. Clinical Cancer Research, 2011

Homologous recombination defects in breast cancer



Roy R, et al. Nat Rev Cancer. 2011 Dec 23;12(1):68-78

- HR deficiency characterizes breast cancers in **BRCA1/2 mutation carriers**
  - Due to loss of heterozygosity at BRCA1 or BRCA2
- HR deficiency implicated in **sporadic TNBC**
  - Methylation
  - Somatic mutation
  - Other epigenetic mechanisms

Twenty years on from the cloning of BRCA1

Potential of individualizing systemic treatment based on germline BRCA1/2 status not yet realized

- **BRCA1/2 germline status currently does NOT factor into systemic therapy decisions**
- **PARP inhibitors have single agent activity in advanced BRCA1/2 mutation-associated breast cancer**
  - NO DRUGS FDA APPROVED
- **Responses to standard chemotherapy drugs in carriers not well characterized**
  - NO DETERMINATION OF BRCA1/2 STATUS IN MOST MAJOR THERAPEUTIC TRIALS, EVEN IN TNBC

Should we use BRCA1/2 mutation status as a biomarker for treatment selection?

- **Strong pre-clinical and early clinical data suggesting high level activity of DNA repair targeted therapeutics**
- **BRCA1/2-deficient breast tumors exhibit differential chemosensitivity compared to BRCA1/2-proficient cancers[1-3]**
  - Greater sensitivity to platinum, doxorubicin, gemcitabine
  - Less sensitivity to taxanes
  - Single agent sensitivity to PARP inhibitors

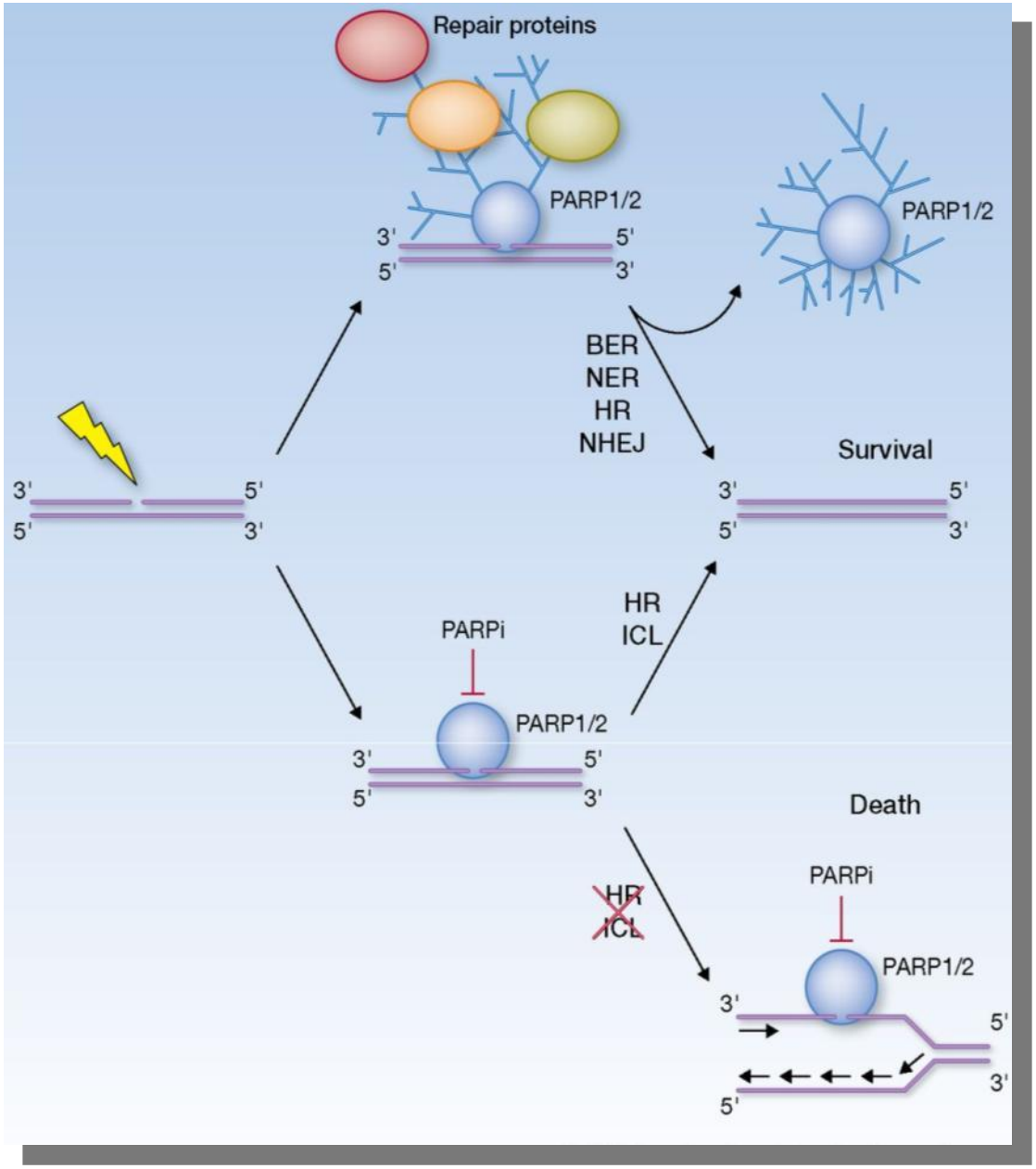
1. Hastak K, et al. Cancer Research, 2010
2. Farmer et al. Nature 434:917 (2005)
3. Bryant et al. Nature 434:913 (2005)

☑ My vote is yes

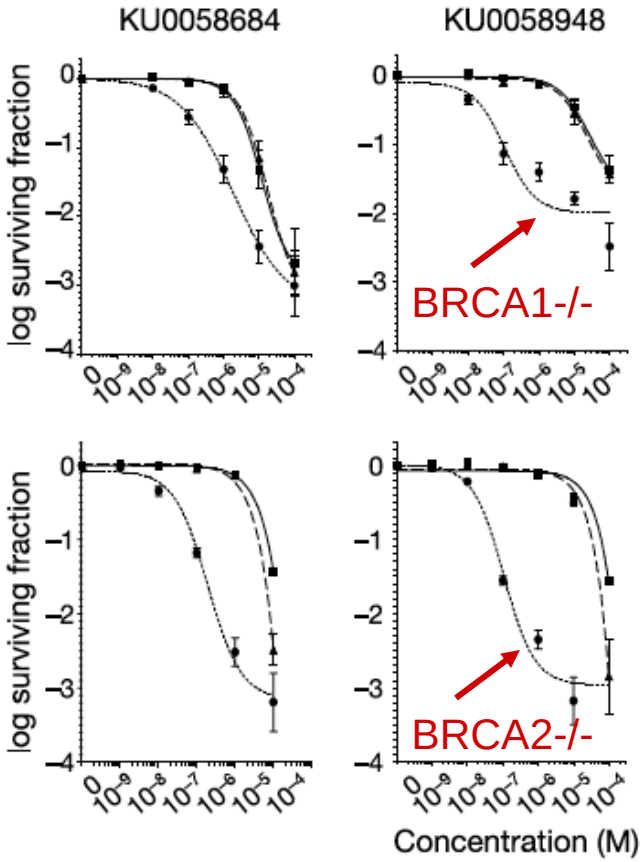
PARP1/2 Function

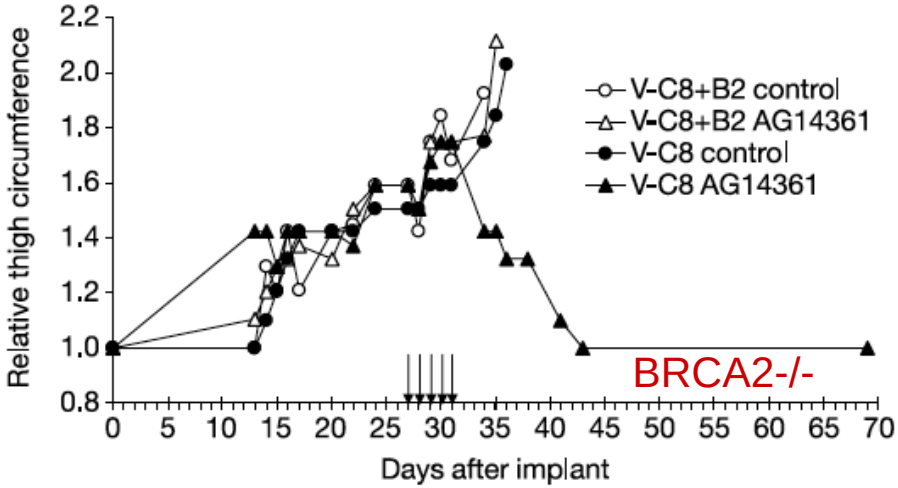
- **Key enzymes involved in repair of single strand DNA breaks**

- **PARP is required for the repair of oxidative DNA damage-associated DNA breaks via base excision repair (BER)**



BRCA1 and 2 deficient cells are markedly sensitive to inhibition of PARP





Loss of BRCA + Loss of PARP1 = "Synthetic Lethal" Interaction

Farmer et al. Nature 434:917 (2005)
Bryant et al. Nature 434:913 (2005)

PARP inhibitiors in advanced BRCA mutant breast cancer: *Initial proof-of-concept*

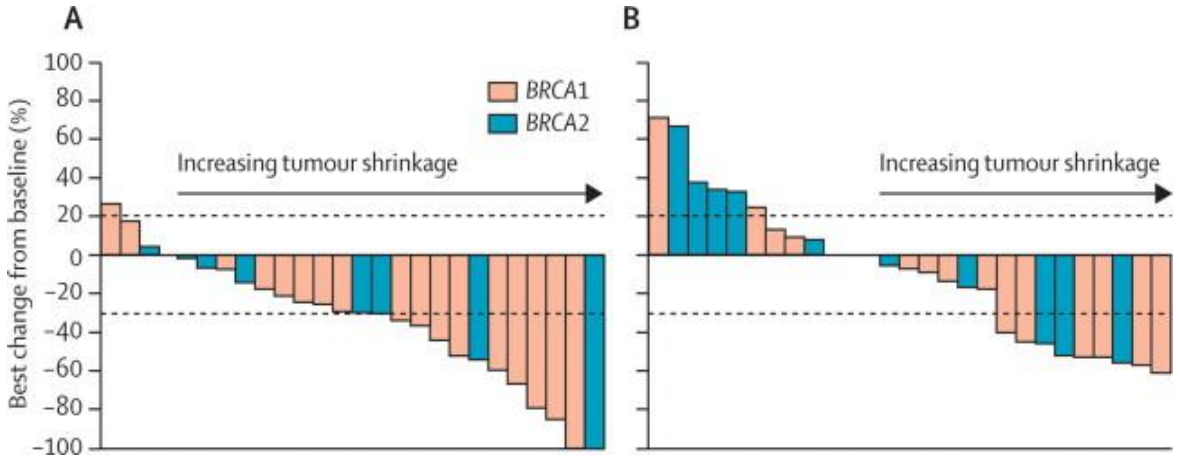
Olaparib: Superior activity at higher dose

	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Objective response	11 (41%; 25–59)	6 (22%; 11–41)
Complete response	1 (4%; 1–18)	0
Partial response	10 (37%; 22–56)	6 (22%; 11–41)
Stable disease	12 (44%; 28–63)	12 (44%; 28–63)
Progressive disease	4 (15%; 6–32)	9 (33%; 19–53)

Data are number (%; 95% CI).

400 mg po BID

100 mg po BID



Tutt A. Lancet. Published online July 6, 2010

PARP inhibitor development in BRCA1/2 mutation-associated breast cancer

- **No FDA approved agents at present… STILL!**
  - Has been difficult for patients to access these drugs despite encouraging data in the heavily pre-treated setting
- **Failure of the phase 3 iniparib study in mTNBC dampened enthusiasm**
  - Realization that this drug was not a bone fide PARP inhibitor did not help
- **Recent increase in randomized clinical trials in BRCA1/2 mutant breast cancer**
  - Combination chemotherapy +/- PARP inhibitor
  - Multiple newer studies of single agent PARP inhibitor versus treatment-of-physician's choice
- **Role of PARP inhibition in sporadic TNBC remains undefined**

PARP inhibitors in advanced clinical development for BRCA1/2+ metastatic breast cancer

Compound	Other names	Phase of testing
Veliparib (AbbVie)	ABT-888	Large Phase II nearing completion (211/255 enrolled) III (upcoming)
Olaparib (AstraZeneca)	KU0059436, AZD2281	III (Not yet open in U.S.)
Niraparib (Tesaro)	MK4827	III ongoing
BMN-673 (BioMarin)		III ongoing Phase II in previously platinum-treated ongoing Phase II for other hereditary mutations upcoming

Platinum in triple-negative breast cancer

Platinum

- **Cisplatin first approved by the FDA in 1978**
  - Noted to have activity in metastatic breast cancer[1]
- **Family of platinum salts bind directly to DNA**
  - Results in formation of DNA-platinum adducts and consequently intra- and inter-strand DNA crosslinks that impede cell division
- **Recent renewed interest in investigating the role of platinum chemotherapy in breast cancer**
  - Hypothesis of greater susceptibility of TN and BRCA1/2 mutant BC to DNA damaging chemotherapeutic agents
  - Limited data in metastatic disease; most important insights from neoadjuvant setting

1. Sledge, et al. JCO, 1988

Platinum in BRCA1/2 mutant breast cancer

- **Proof-of-concept neoadjuvant study of 25 BRCA1 mutation carriers (80% TNBC)[1]**
  - **pCR rate of 72%** with single agent cisplatin 75 mg/m^2 every 21 days x 4
- **Rate of pCR to standard anthracycline/taxane-based therapy in BRCA1/2 carriers not well known**
  - Retrospective data from USA: **pCR of 37% versus 31%** in BRCA1/2 positive vs. negative TNBC pts treated with AC +/-T[2]
  - Retrospective data from Israel: **pCR of 67% vs. 37%** in BRCA1/2 positive vs. negative TNBC treated with AC-T dose dense

1. Gronwald, et al. JCO, 2009 (abstract); 2. Arun B, et al. JCO, 2011; 3. Paluch-Shimon, et al; ASCO 2014 Abstract 1023

Randomized phase II neoadjuvant "add-on" carboplatin studies in unselected TNBC

Study	n	Regimen	pCR (%)
Alba ***GEICAM 2006-03***	**94**	**Epirubicin** 90 mg/m2 + **cyclophosphamide** 600 mg/m2 q21 days x 4 cycles followed by **docetaxel** 100mg/m2 q21 days x 4 or **docetaxel** 75 mg/m2 + **carboplatin** AUC 6 every 21 days x 4 cycles	**30% with Cp** **30% no Cp**
von Minckwitz ***GeparSixto***	**315**	**Paclitaxel** 80 mg/m2 every 7 days + **non-pegylated liposomal doxorubicin** 20 mg/m2 every 7 days + **bevacizumab** 15 mg/kg IV every 21 days +/- **carboplatin** AUC 1.5 every 7 days x 18 cycles	**53% with Cp** **37% no Cp**
Sikov ***CALGB 40603***	**443**	**Paclitaxel** 80 mg/m2 every 7 days x 12 cycles followed by **doxorubicin** 60 mg/m2 + **cyclophosphamide** 600 mg/m2 every 2 weeks x 4 cycles +/- **carboplatin** AUC 6 every 21 days x 4 cycles (with paclitaxel) +/- **bevacizumab** 10 mg/ kg every 2 weeks x 9 cycles (with paclitaxel and doxorubicin/cyclophosphamide)	**54% with Cp** **41% no Cp** **52% with Bev** **44% no Bev**

A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto – GBG 66)

Gunter von Minckwitz, Andreas Schneeweiss, Christoph T. Salat, Mahdi Rezai, Dirk M. Zahm, Peter Klare, Jens U. Blohmer, Hans Tesch, Fariba Khandan, Sebastian Jus, Christian Jackisch, Keyur Mehta, Valentina Nekljudova, Sibylle Loibl, Michael Untch

for the

GBG/AGO-B study groups

AGO-B BREAST STUDY GROUP

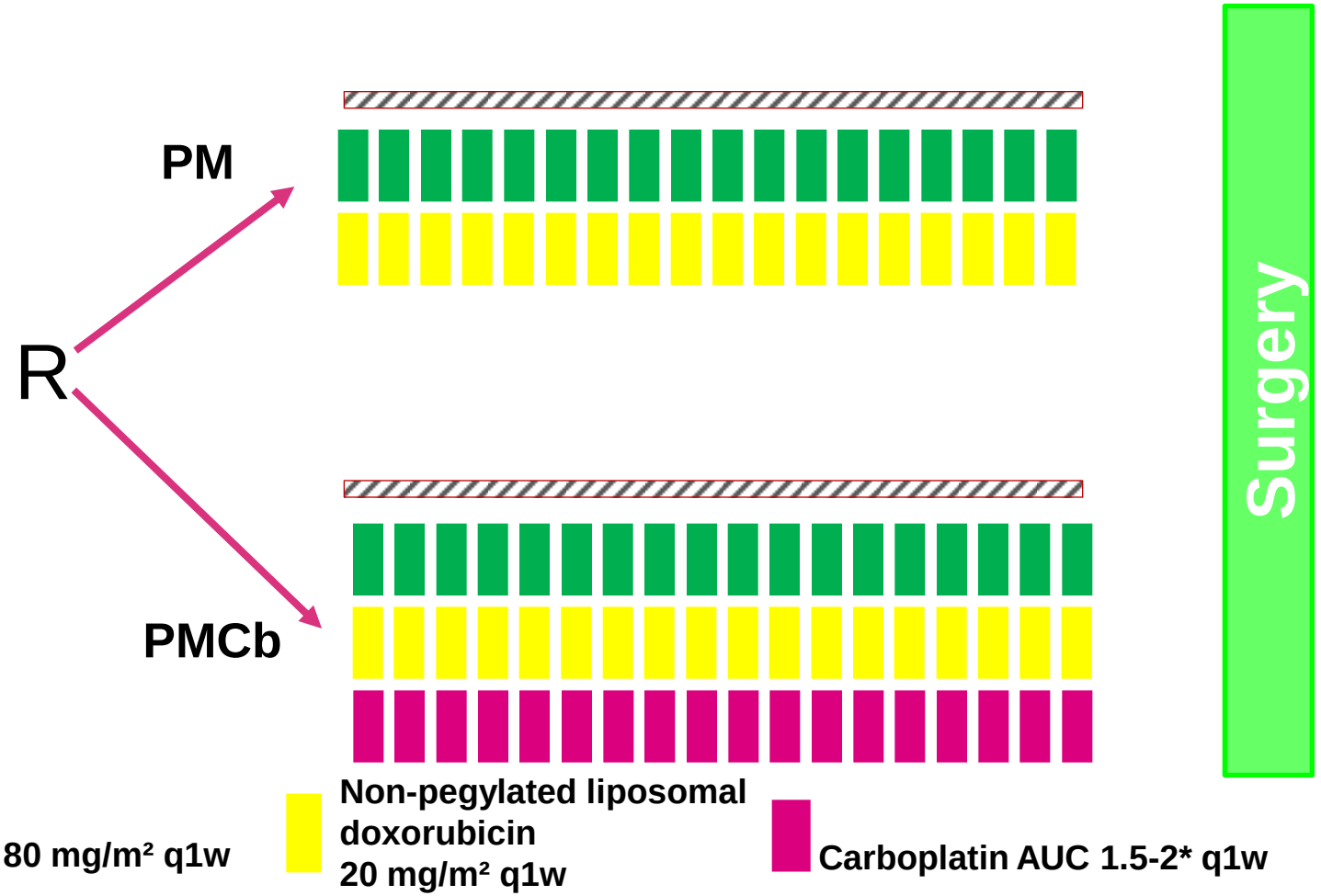
GBG GERMAN BREAST GROUP

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.

Therapy in TNBC subgroup

N=315

centrally confirmed TNBC



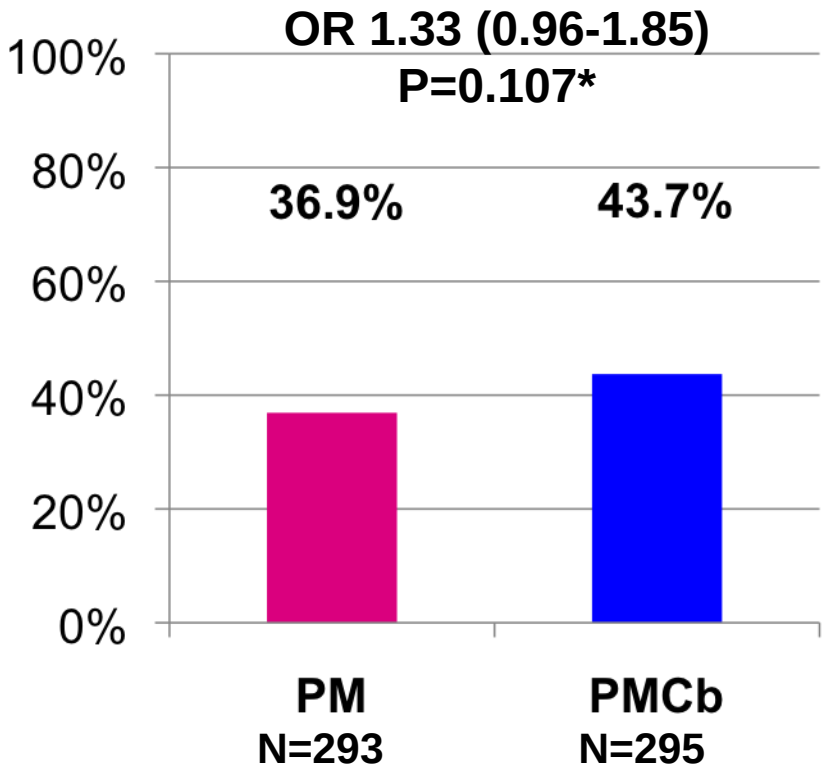
TNBC: Bevacizumab 15 mg/kg q3w

von Minckwitz et al. Lancet Oncology, May 2014

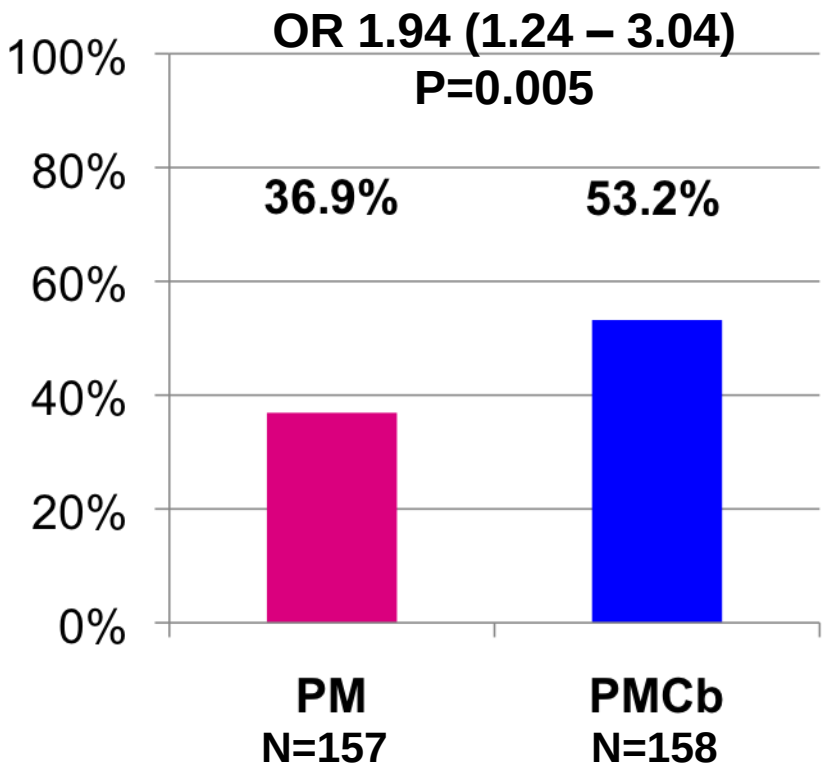
pCR Rates Overall and in TNBC Subgroup

ypT0 ypN0

Overall



TNBC



*Phase II significance level < 0.02

AGO-B BREAST STUDY GROUP

von Minckwitz et al. Lancet Oncology, May 2014

GBG GERMAN BREAST GROUP

Discontinuations common and primarily due to adverse events

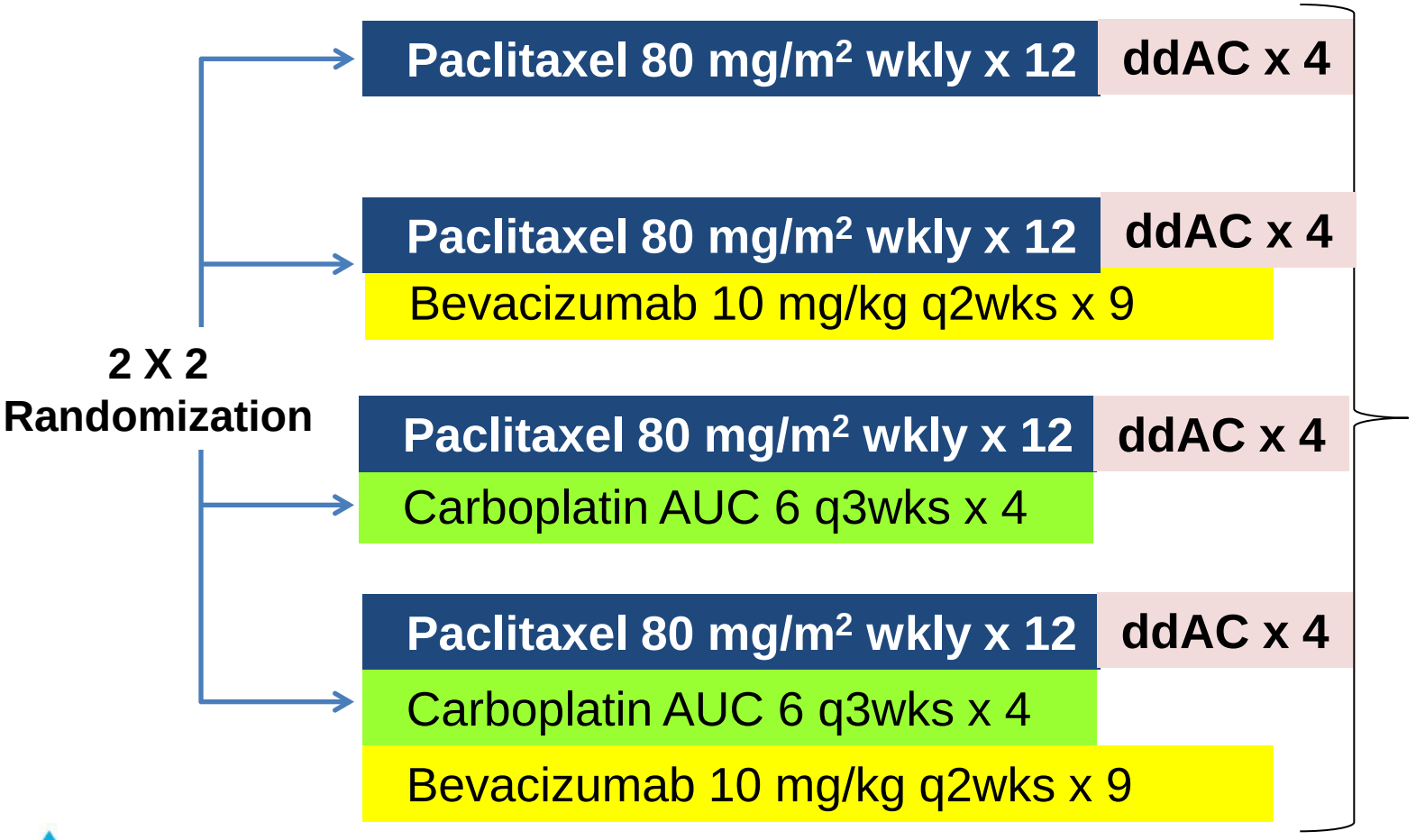
	PM	PMCb
	N	N
Randomized	299	296
Started treatment	293	295
	%	%
Discontinued all treatments		
➢ adverse event	31.5	37.7
➢ investigator‘s decision	2.1	2.8
➢ patient’s wish	3.5	5.2
➢ progressive disease	0.7	1.7
➢ death*	1.4	0.3
Completed 6 cycles of treatment	60.9	52.2

*PM: TNBC: acute myocardial infarction (1), febrile neutropenia (1); HER2+: asystole (1), pneumonia (1)
PMC: TNBC: sepsis after port infection (1)

Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant weekly paclitaxel followed by dose-dense AC on pathologic complete response rates in triple-negative breast cancer: CALGB/Alliance 40603

William M Sikov, Donald A Berry, Charles M Perou, Baljit Singh, Constance Cirrincione, Sara Tolaney, Charles S Kuzma, Timothy J Pluard, George Somlo, Elisa Porte, Mehra Golshan, Jennifer R Bellon, Deborah Collyar, Olwen M Hahn, Lisa A Carey, Clifford Hudis, and Eric P Winer for the CALGB/Alliance

CALGB 40603: Schema – Randomized Phase II

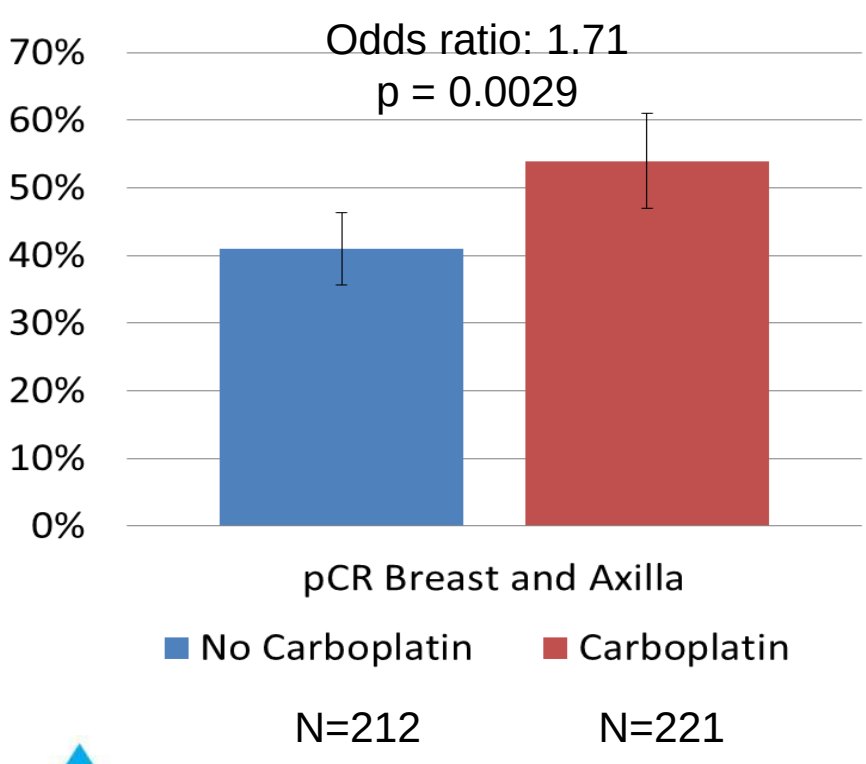


ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

pCR Breast/Axilla (ypT0/is N0)

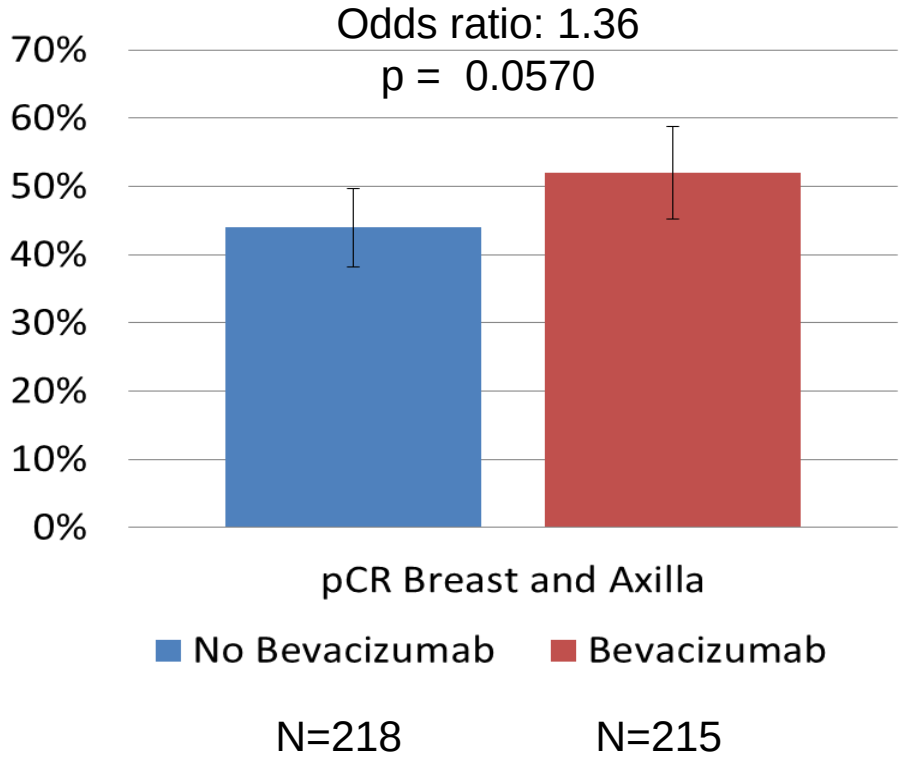
+/- Carboplatin

41% (35-48%) | **54%** (48-61%)



+/- Bevacizumab

44% (38-51%) | **52%** (45-58%)



Recent TNBC platinum data in context

- **Two recent P2 randomized carboplatin studies positive**
  - GEICAM / 2006-03 negative
- **GeparSixto and CALGB 40603 show increase in pCR with carboplatin**
  - In both studies, bevacizumab was also included
- **In the randomized phase III GeparQuinto trial, bevacizumab increased pCR in the TNBC subset**
  - **EC-Docetaxel:** **pCR = 27.9%** **Δ11.4%**
  - **EC-Docetaxel + Bev** **pCR = 39.3%**
- **Looking at individual arms in CALGB 40603**
  - **T-AC** **pCR 39%**] **Δ10%**
  - **TCp-AC** **pCR 49%**]
  - **TCpB-ACB** **pCR 60%**] **Δ11%**

Recent TNBC platinum data in context

- **We know bevacizumab increases pCR by ~10%, but does not add benefit in adjuvant TNBC treatment**
  - Phase III BEATRICE study showed no improvement in DFS or OS with adjuvant bevacizumab in TNBC
- **Need to consider the chance that platinum (like bev) will not add DFS/OS benefit in a definitive phase III carboplatin TNBC trial**
  - Additive toxicity also a significant concern
- **Highlights need for biomarkers of platinum response**
  - Candidates: Germline BRCA mutation status
    ‘Genomic scar’ due to HR defects
    Tumor lymphocytic infiltration

Pathological complete response (pCR) rates after carboplatin-containing neoadjuvant chemotherapy in patients with germline BRCA (gBRCA) mutation and triple negative breast cancer (TNBC) – Results from GeparSixto

Abstract # 1005

Gunter von Minckwitz, Eric Hahnen, Peter A. Fasching, Jan Hauke, Andreas Schneeweiss, Christoph T. Salat, Mahdi Rezai, Jens U. Blohmer, Dirk M. Zahm, Christian Jackisch, Bernd Gerber, Peter Klare, Sherko Kümmel, Holger Eidtmann, Stephan Paepke, Valentina Nekljudova, Sibylle Loibl, Michael Untch, Rita Schmutzler for the GBG/AGO-B study groups

AGO-B
BREAST STUDY GROUP

GBG
GERMAN
BREAST
GROUP

GeparSixto: BRCA1/2 & RAD mutation carriers achieve superior pCR rates

- **Germline blood was available for 294 of 315 TNBC pts**
  - **BRCA1/2 mutations were detected in 41 patients using a number of methods**
  - **RAD50/RAD51c mutations were detected in 3 patients**
  - **164 patients incompletely genotyped**

- **Considering all randomized patients with TNBC (n=294)**
  - **pCR among B1/2 + RAD carriers = 54.5%**
  - **pCR among B1/2 + RAD non-carriers = 41.6%**

    Δ 12.9%; p=0.11
  - **pCR among B1/2 + RAD non-carriers with +FH = 44.3%**
  - **pCR among B1/2 + RAD non-carriers with no FH = 40.4%**

    Δ 3.9%

von Minckwitz et al. ASCO 2014, abstract 1005

Platinum response by family history & germline HR pathway mutation status

	PM	PMCb	OR	p
% pCR	(N=146)	(N=149)		
No family history	34.5	46.0	1.61	0.08
		Δ 11.5		
Family history of BC/OC without mutation (n=79)	30.8	57.5	3.04	0.02
		Δ 26.7		
g*BRCA/RAD* mutation with/without family history	43.5	66.7	2.60	0.13
		Δ 23.2		

AGO-B BREAST STUDY GROUP

von Minckwitz et al. ASCO 2014, abstract 1005

GBG GERMAN BREAST GROUP

Carboplatin benefit among those with FH *lacking* a germline B1/2 or RAD mutation fascinating

- **Due to as yet undiscovered BRCA1/2 mutations?**
  - **>50% yet to have comprehensive B1/2 genotyping**
- **Due to germline mutations in other homologous recombination DNA repair pathway genes?**
  - **Excellent opportunity to assess additional HR pathway genes in this trial**

Breast Cancer Genes: The Landscape

Additional germline biomarkers?

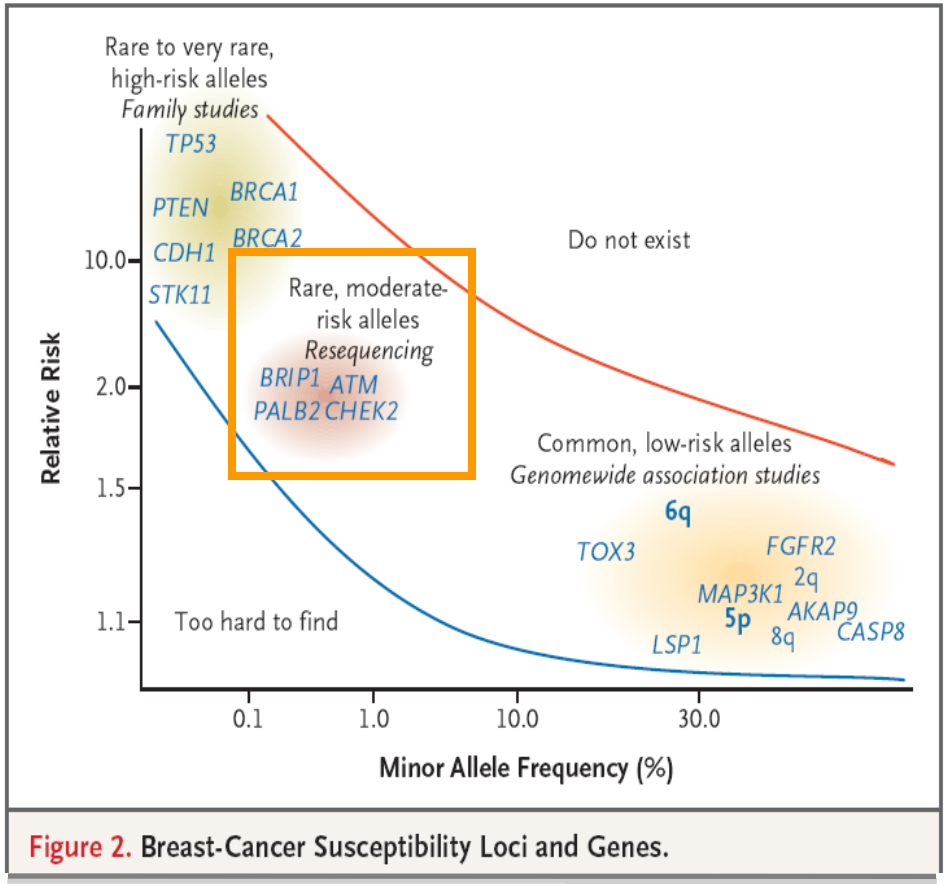


Figure 2. Breast-Cancer Susceptibility Loci and Genes.

- **Many other genes implicated in familial breast cancer[1]**
  - Many in homologous recombination pathway
- **In women testing negative for BRCA1/2 mutations**
  - Multi-gene sequencing identifies an additional ~10% with pathogenic germline mutations[2]
- **DNA repair-targeted therapy is hypothesized to have a role in these patients with non-B1/2 germline HR alterations**

1. Foulkes N Engl J Med 2008
2. Kurian AW, et al J Clin Oncol 2014

Rise of the germline multiplex panel

	Ambry Genetics*				University of Washington Laboratory Medicine†	
Gene	CancerNext	BreastNext	ColoNext	OvaNext	BROCA	ColoSeq
APC	●		●		●	●
ATM	●	●		●	●	
ATR					●	
BABAM1					●	
BAP1					●	
BARD1	●	●		●	●	
BMPR1A			●		●	
BRIP1	●	●		●	●	
CDH1	●	●	●	●	●	●
CDK4					●	
CDKN2A					●	
CHEK1					●	
CHEK2	●	●	●	●	●	
FAM175A/Abraxas					●	
MLH1	●		●	●	●	●
MRE11A	●	●		●	●	
MSH2-positive *EPCAM*	●		●	●	●	●
MSH6	●		●	●	●	●
MUTYH	●	●	●	●	●	●
NBN	●	●		●	●	
PALB2	●	●		●	●	
PMS2	●		●	●	●	●

Domchek SM, et al. Multiplex genetic testing for cancer susceptibility. JCO:2013;31:p1268

Identifying cause or consequence:

Which will prove the better biomarker?

PrECOG 0105: Final efficacy results from a phase II study of gemcitabine & carboplatin plus iniparib (BSI-201) as neoadjuvant therapy for triple - negative and BRCA1/2 mutation-associated breast cancer

Telli ML, Jensen KC, Kurian AW, Vinayak S, Lipson JA, Schackmann EA, Wapnir I, Carlson RW, Sparano J, Head B, Goldstein LJ, Haley B, Dakhil S, Manola J & Ford JM

Results PrECOG 0105

Intent-to-treat population

Pathologic Response (n=80)				
	All patients **n = 80**	**BRCA 1/2 wild-type** **n = 61**	**BRCA 1/2 mutant** **n = 19**	**TN & BRCA 1/2 mutant** **n = 16**
pCR [RCB 0]; n (%)	**29 (36%)**	**20 (33%)**	**9* (47%)**	**9* (56%)**
90% CI	27–46	23–44	27-68	33-77
RCB 0/1; n (%)	**45 (56%)**	**31 (51%)**	**14 (74%)**	**12 (75%)**
90% CI	46-66	40-62	52-89	52-91

* One BRCA1 carrier had bilateral TNBC & achieved pCR in both breasts

Homologous Recombination Deficiency (HRD) Assay

Goal:

- **To detect a genomic HR deficiency *'footprint'* in a tumor caused by various defects in the HR pathway**
  - Potential to identify non-BRCA1/2 mutation carriers with 'BRCA-like' cancers who may benefit from DNA repair targeted treatment strategies

Assay development:

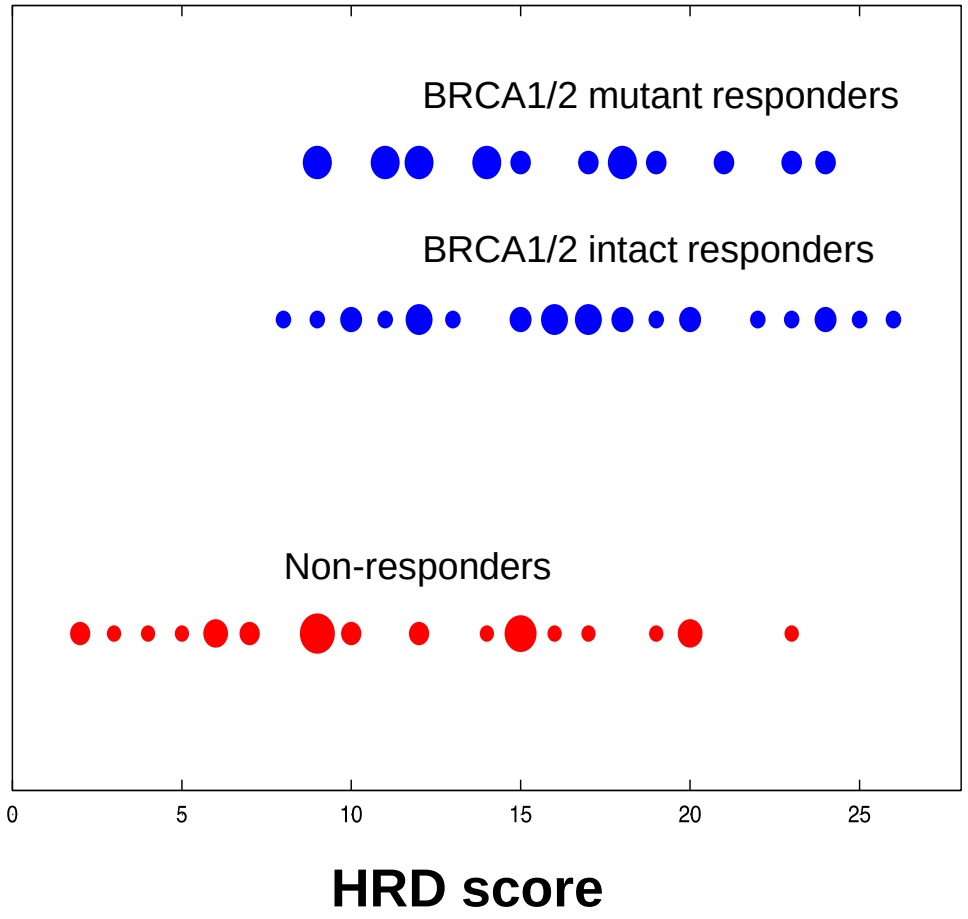
- **Association of genomic patterns of loss of heterozygosity (LOH) & HR deficiency assessed in ovarian cancer**

Major Finding:

- **LOH regions of intermediate size were observed more frequently in tumors with defective BRCA1 or BRCA2**
  - **HRD Score = Count of the # of LOH regions of intermediate size (> 15 Mb and < whole chromosome) observed in the tumor genome**

Abkevich V, et al. British Journal of Cancer, 2012

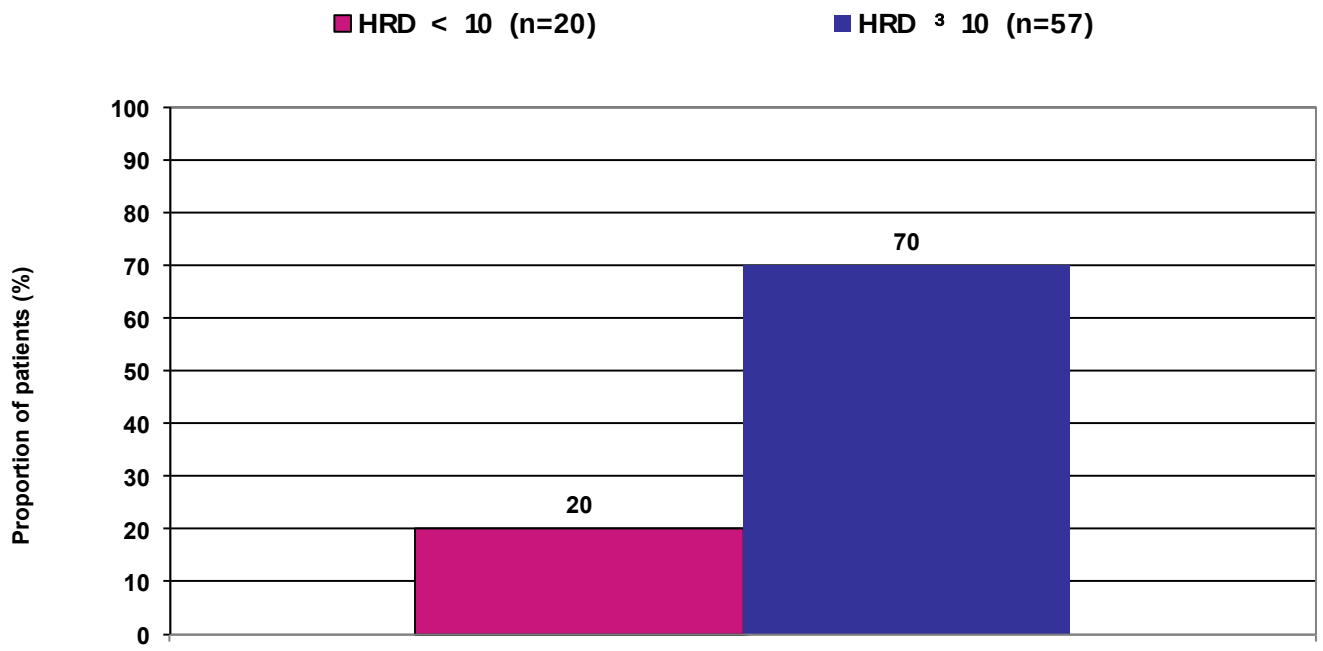
Pathologic response by HRD Score



Association of HRD Score & Response (n=77)		
Mean HRD Scores: All patients (n=77)		
Responders	16.2	p=0.0003
Non-responders	11.2	
Mean HRD Scores: BRCA1/2 intact (n=58)		
Responders	16.6	p=0.0006
Non-responders	11.1	
Correlations between response and clinical stage, grade not significant		

Telli ML, Timms K, Hartmann A-R, Ford JM, et al. SABCS 2012; abstract PD09-04

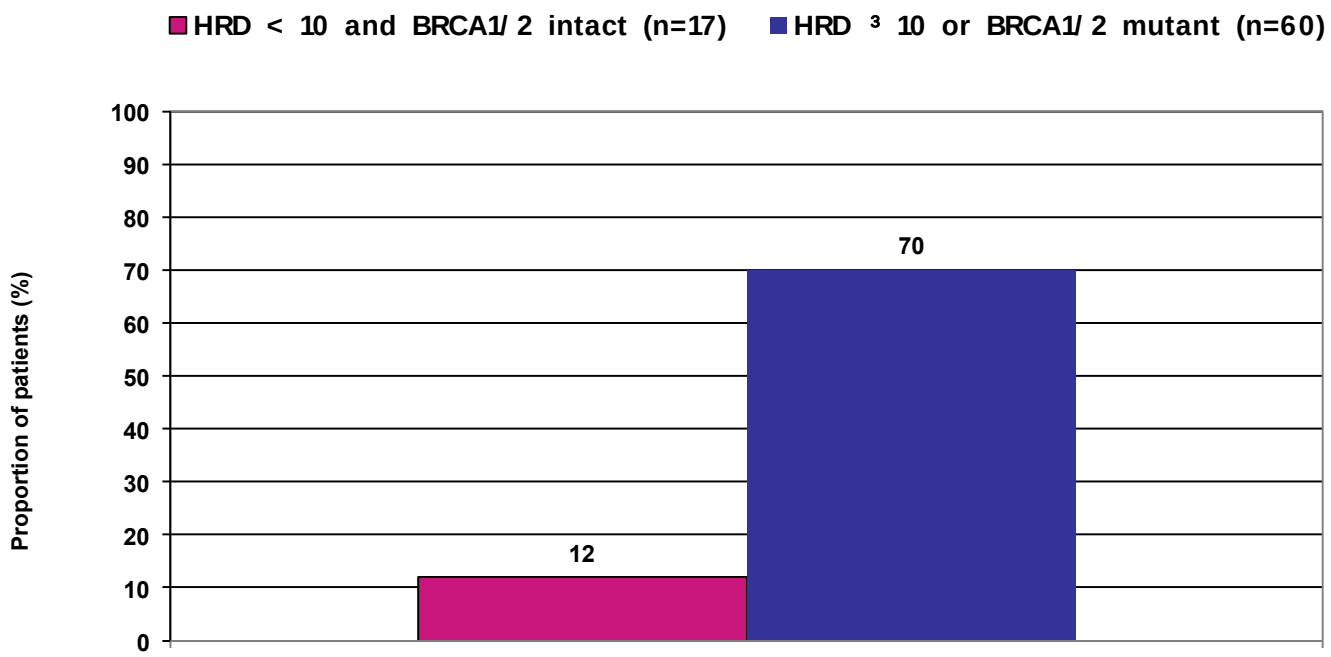
Favorable response (RCB 0/1) by HRD Score



p = 0.0001

Telli ML, et al. SABCS 2012

Favorable response (RCB 0/1) by HRD Score & BRCA1/2 Status



p = 0.00002

Telli ML, et al. SABCS 2012

Role of Platinum in Metastatic TNBC

Platinum in metastatic TNBC

- **<u>Randomized</u> data comparing platinum to other standard chemotherapies are lacking**

- **Cross-study comparisons difficult**
  - Few TNBC specific trials -> mostly subsets
  - Various “triple-negative” definitions
  - BRCA1/2 genotype largely unassessed
  - TNBC is heterogeneous -> varying chemosensitivity
  - Disease-free interval important in this disease and not always adjusted for in trials

Platinum in unselected mTNBC

Regimen	n	ORR (%)	PFS (months)	Prior Chemo (%)	Disease-free interval (median)
Gemcitabine / Carboplatin[1]	**258**	**30%**	**4.1**	**90%**	**15 mos**
1st line	*148*		*4.6*		*15.9 mos*
2nd/3rd line	*110*		*2.9*		*13.8 mos*
Carboplatin or cisplatin[2]	**86**	**26%**	**2.9**	**86%**	**NA**
1st & 2nd line			ORR in BRCA1/2 mutant **55%** vs. **20%** in BRCA1/2 wild-type		

1. O'Shaughnessy J, et al. ASCO 2011 (abstract)
2. Isakoff S, et al. ASCO 2014 (abstract 1020)

KING'S College LONDON
University of London

ICR The Institute of Cancer Research

TNT

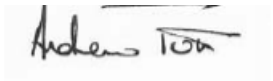
Triple Negative breast cancer Trial

A randomised phase III trial of carboplatin compared to docetaxel for patients with metastatic or recurrent locally advanced ER-, PR- and HER2- breast cancer.

Incorporating the BRCA Trial

Main REC Reference Number: 07/Q0603/67
ISRCTN: ISRCTN97330959
EudraCT Number: 2006-004470-26
Protocol Number: ICR-CTSU/2006/10003
CRUK Number: CRUK/07/012
CTA Number: 22138/0004/001-0001

Dr Andrew Tutt (Chief Investiga



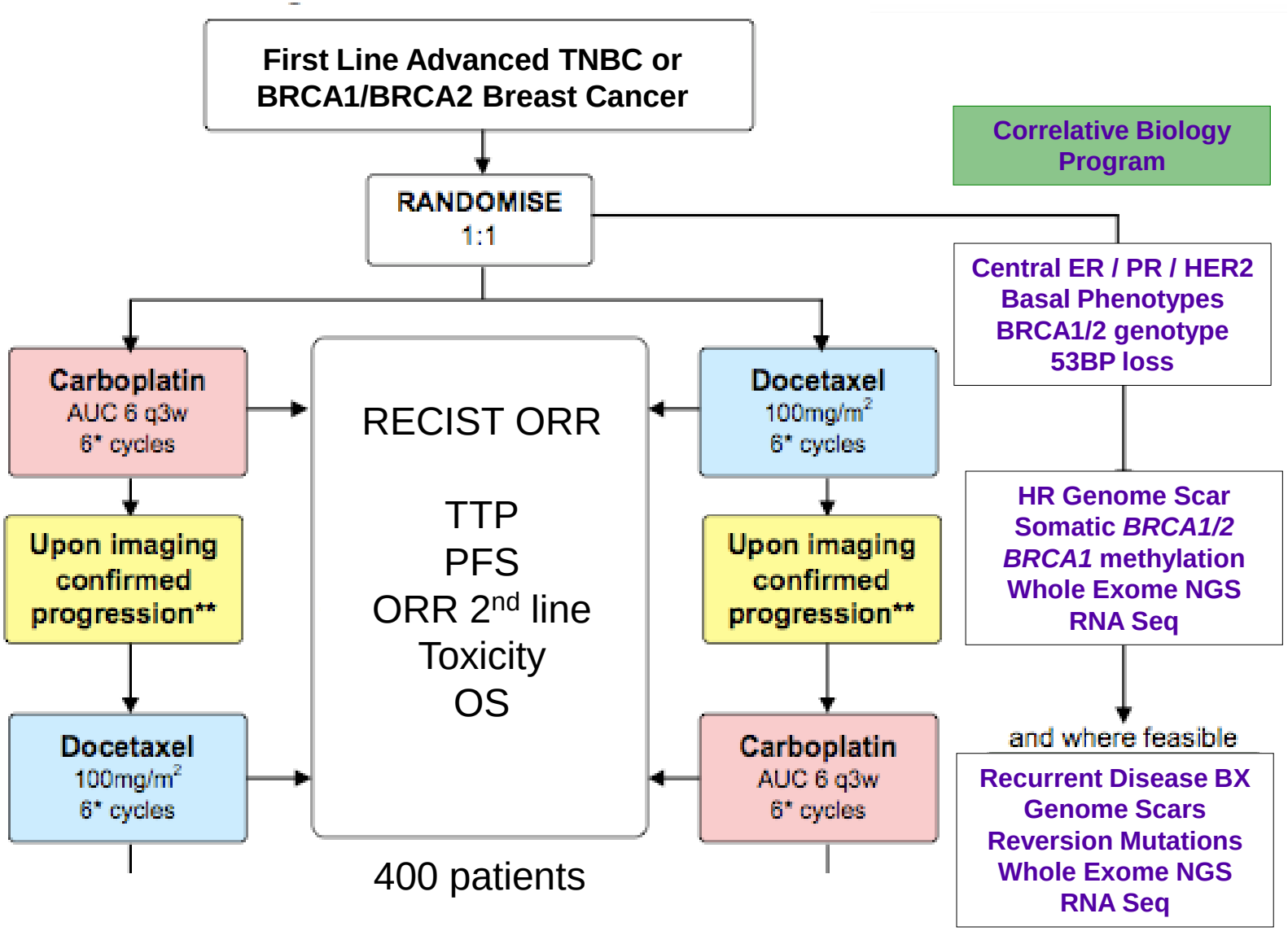
Completed Accrual 2014
400 patients
80 UK centres

BREAST CANCER BREAKTHROUGH

CANCER RESEARCH UK

NCRI National Cancer Research Institute

TNT / BRCA Trial



Emerging concepts in immunotherapy

Association of increased tumor-infiltrating lymphocytes (TILs) with immunomodulatory (IM) triple-negative breast cancer (TNBC) subtype and response to neoadjuvant platinum-based therapy in PrECOG 0105

Abstract 1000

Shaveta Vinayak, Robert Gray, Sylvia Adams, Kristin C. Jensen, Judi Manola, Anosheh Afghahi, Lori J. Goldstein, James M. Ford, Sunil S. Badve

& Melinda L. Telli

Results: TILs significantly associate with pathologic response by RCB value in multivariate models

Covariate	sTILs (p value)	iTILs (p value)
Age	NS	NS
T size by MRI	0.01	NS
N stage	NS	0.05
Tumor grade	NS	NS
gBRCA status	0.02	0.05
sTILs (increase of 10%)	**0.02**	
iTILs (increase of 10%)		**0.009**

For every 10% **increase** in **sTILs**, there is an expected **lowering** of 0.17 in RCB value
For every 10% **increase** in **iTILs**, there is an expected **lowering** of 0.50 in RCB value

Multivariate model using pCR:
sTILs were not significant in this model
For every 10% **increase** in **iTILs**, there is an expected **increase** of 162% in the odds of pCR

Presented by: Shaveta Vinayak, M.D., M.S.

Lessons learned from mice (and applied to men)

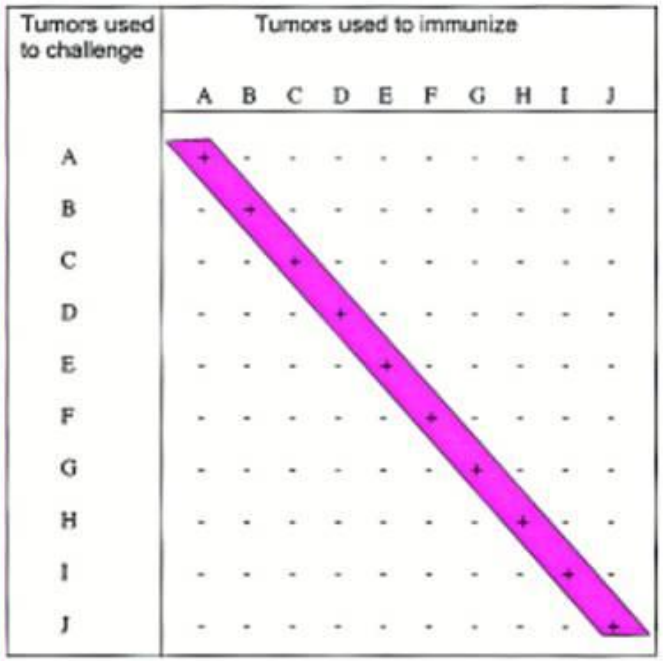


Figure 1. Individually Distinct Immunogenicity of Cancers

Immunization with a particular cancer elicits the most potent protective immunity to the specific cancer used for immunization and not to other cancers, even if the tumors are induced by the same carcinogen and are of the same histological origin (see Gross, 1943; Prehn and Main, 1957; Klein et al., 1960; Old et al., 1962; Globerson and Feldman, 1964; Basombro, 1970).

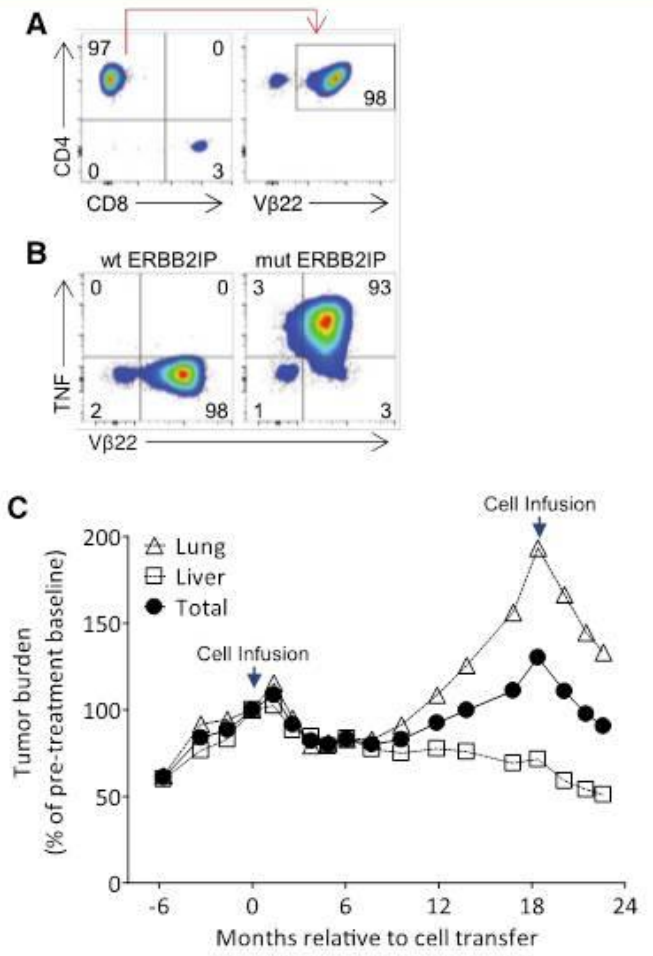
Srivastava et al. Immunity 1998
Srivastava and Old. Immunology Today 1988

In Mice …

- Each tumor is immunologically unique.[1,2]
- One aspect of a tumor's unique-ness comes from random, tumor specific mutations.[3-4]
- Some tumor specific mutations can be recognized by the immune system (neo-antigen).[5]
- These neo-antigens can mediate tumor rejection.[6-9]

1. Srivastava et al. Immunity. 1998 2. Srivastava and Old. Immunology Today. 1988 3. Srivastava. Adv Cancer Res. 1993 4. Duan et al. Cancer Res. 2008 5. Many examples see http://cancerimmunity.org/peptide/mutations/ 6. Dubey et al. JEM. 1997 7. Ikeda et al. PNAS. 1997 8. Matsutake et al. PNAS. 2001 9. Matsushita et al. Nature. 2012

Lessons learned from mice (and applied to men)



Tran et al. Science 2014

In Men …

- Human tumors harbor 100's – 1000's of mutations and 10'-100's of these are predicted to represent neo-antigens.[1,2]
- Immune responses in cancer patients include T cells specific for some mutated proteins.[3]
- Responses to neo-antigens may be associated with activity of ipilimumab.[4]
- T cells specific for a neo-antigen can mediate tumor rejection.[5]

[1]Segal et al. Cancer Res. 2008 2. Srivastava and Srivastava. PLoS 2009 3. Many examples see http://cancerimmunity.org/peptide/mutations/ 4. Van Rooij et al. J Clin Oncol 2013 5. Tran et al. Science. 2014.

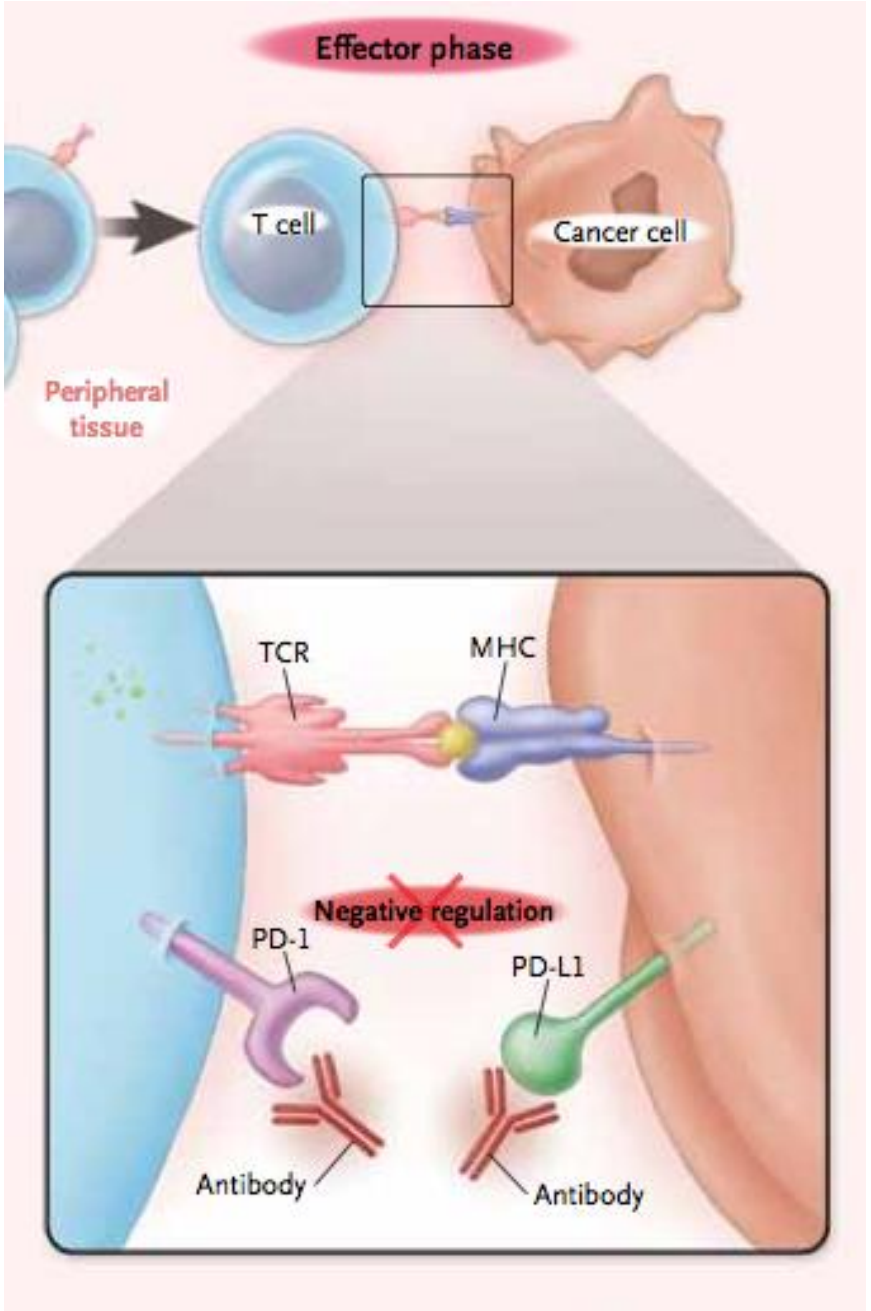
Presented by: Margaret Callahan

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Are BRCA1/2 tumors more immunogenic due to higher levels of mutations?

- **BRCA1 and BRCA2 mutation-associated tumors contain high levels of genome instability due to defects in normal DNA repair**
  - With increasing mutational burden, there is increased potential that the immune system will recognize a neo-antigen in the tumor
- **Could this increased burden of neoantigens render BRCA1/2 tumors more amenable to immunotherapies?**
  - No answers yet, but very hot topic
  - Stay tuned

- **Programmed death 1 (PD-1) is expressed on T cells**
  - Inhibits killing by T cells when binds to PD-L1
  - PD-L1 expressed on tumors or in the tumor microenvironment
- **Many antibody drugs now targeting PD-1 and PD-L1**
  - Impressive activity in melanoma, kidney cancer, lung cancer, others



Ribas A. N Engl J Med 2012; 366:2517-2519

PD-L1 and BRCA1

- **Recently reported study showed that 7/7 BRCA1 mutant tumors also expressed PD-L1[1]**
  - ~20% positive in unselected TNBC[2]

- **Elevated PD-L1 expression in TNBC was significantly associated with DNA repair genes[1]**
  - Low expression of BRCA1
  - Low expression of FANCA

1. Pockaj B, et al. ASCO 2014, abstract 1001
2. Mittendorf E, et al. Cancer Immunol Res. 2014 Apr;2(4):361-70

Summary

- **Growing evidence that platinum-based therapy is active in both advanced & early-stage TNBC**
  - Not yet practice changing in early breast cancer
  - Randomized data urgently needed in mTNBC
- **Efficacy influenced by BRCA1/2 mutation status**
  - BRCA1/2 mutation carriers achieve higher response rates
  - This information needs to be more routinely captured in trials
- **Beyond BRCA1 and BRCA2, other germline biomarkers associated with therapeutic sensitivity likely exist**
  - Studies needed in this space

Summary

- **Certain sporadic TNBC patients likely stand to benefit significantly from a platinum-based approach**

- **Ultimately, measures of global genomic instability (e.g. HRD) may have the greatest potential to identify those patients who stand to benefit most from a DNA repair defect-targeted approach**

- **Immunotherapy approaches may prove relevant for TN & BRCA1/2+ breast cancer**
  - Urgently need clinical trials in this space

Careful randomized clinical trial designs that incorporate biomarkers of response are key

Thank you!