Triple-Negative Breast Cancer

William J. Gradishar MD

Betsy Bramsen Professor of Breast Oncology

Director, Maggie Daley Center for Women's Cancer Care

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NORTHWESTERN UNIVERSITY
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Search of Clinical Trials.Gov Using Search Term "Triple Negative Breast Cancer"

(accessed 10/25/12)

- Number of trials
  - 105 active trials (51 specific for TNBC), 15 phase III trials
- Selected adjuvant phase III trials
  - BEATRICE (N=2581) - adjuvant chemotherapy +/- bevacizumab
  - TITAN (N=1800) - AC → weekly paclitaxel x 12 vs. ixabepilone x 4
  - PACS08 (N=2500) - FEC100 x 3 → docetaxel x 3 vs. ixabepilone x 3
  - Spanish Breast Cancer Group (N=876) – AC-T +/- capecitabine
  - China (N=520) – FEC → docetaxel vs. doc/capecitabine→ capecitabine + EC
  - China (N=600) – AC-T +/- capecitabine
  - China (N= 500) – Docetaxel/carbo vs. EC→docetaxel
- Neoadjuvant trials
  - C40603 (400): Paclitaxel (+/-carbopatin) → AC (+/- bevacizumab)
  - Neo-TN (N=270) – AC→docetaxel/capecitabine vs. high-dose alkylators
  - GeparSixto (N=600) – AC-taxane +/- carboplatin
  - China (N=600) – TAC vs. TC
- Metastatic trials
  - China (N=232) – Gemcitabine/cisplatin vs. gem/paclitaxel
  - UK (N=400) – Carboplatin vs. docetaxel

Search of Clinical Trials.Gov Using Search Term "Triple Negative Breast Cancer" - Novel Agents

(accessed 10/25/12)

- Met inhibitor: ARQ197, Onartuzumab (Metmab), foretinib
- PI3K and/or inhibitor: BKM 120, temsirolimus (+neratinib)
- HDAC inhibitors: entinostat, vorinosat
- Demethylating agents: azacitidine (+entinostat)
- PARP inhibitors: ABT-888, E7449
- Angiogenesis inhibitor: cediranib (+olaparib), ramicurumab, IMC18F1, foretenib, sorefenib
- Hsp90 Inhibitors: ganetespib
- Aurora kinase inihbitors: ENMD 2076
- EGF inhibitorsR: erlotinib (+metformin,), apatanib
- MEK inhibitors: GSK1120212
- Wnt innibitor: LGK974
- CDK inihbitor: Dinaciclib, P276-00
- FMS-Kit inihbitor: PLX3397
- Aptoptosis inducer: LCL161 (deactivating inhibitor of apoptosis proteins (IAPs),
- Immunotherapy: MUC1 vaccine, adoptive cellular therapy (DC-CIK)
- Cytotoxics: SN38 -NK012, AEZS-108 (LHRH-dox)

Epidemiology and Clinical Presentation

Triple-Negative Disease Compared with Other Phenotypes in the California Cancer Registry Study

Bauer et al. Cancer 2007: 109; 721

- Population-based study
  - 6370 with "triple-negative" disease compared with 44,704 "other" cases (12% of all cases)
- Findings – more likely to be associated with
  - Younger age (<40): OR 1.53
  - Non-Hispanic black (OR 1.77) or Hispanic (OR 1.23
  - Higher grade (72% grade 3)
  - Poorer 5 year RFI irrespective of stage
    - TNBC: 76% (similar to 76% for HER2-Pos)
    - HR-Pos, HER2-Neg: 94%

Characteristics of Triple Negative Breast Cancer

- Usually poor histologic grade
- Presents with larger tumor size but less commonly associated with nodal metastases
- Commonly associated with BRCA mutations
- Early relapse (< 5 years of diagnosis)
- Relapse in visceral sites and CNS
- Usually basal genotype in gene expression profiling

Clinicopathologic Features, Patterns of Recurrence, and Survival Among Women With Triple-Negative Breast Cancer in the National Comprehensive Cancer Network

Nancy U. Lin, MD[1]; Ann Vanderplas, MS[2]; Melissa E. Hughes, MSc[3]; Richard L. Theriault, DO, MBA[4]; Stephen B. Edge, MD, FACS[5]; Yu-Ning Wong, MD, MSCE[6]; Douglas W. Blayney, MD[7,8]; Joyce C. Niland, PhD[2]; Eric P. Winer, MD[1]; and Jane C. Weeks, MD, MSc[1,3]

	Triple Negative vs HR+/HER2−		HER2+ vs HR+/HER2−	
Site[b]	OR (95% CI)	*P*	OR (95% CI)	*P*
Locoregional vs other	1.32 (1.01-1.74)	.045	1.12 (0.83-1.51)	.45
Lung vs other	2.17 (1.47-3.21)	<.001	1.73 (1.13-2.66)	.012
Brain vs other	3.50 (2.10-5.85)	<.001	3.97 (2.35-6.72)	<.001
Bone vs other	0.26 (0.19-0.36)	<.001	0.39 (0.29-0.54)	<.001
Liver vs other	1.09 (0.74-1.61)	.67	1.58 (1.07-2.33)	.02

Lin et al. Cancer 2012

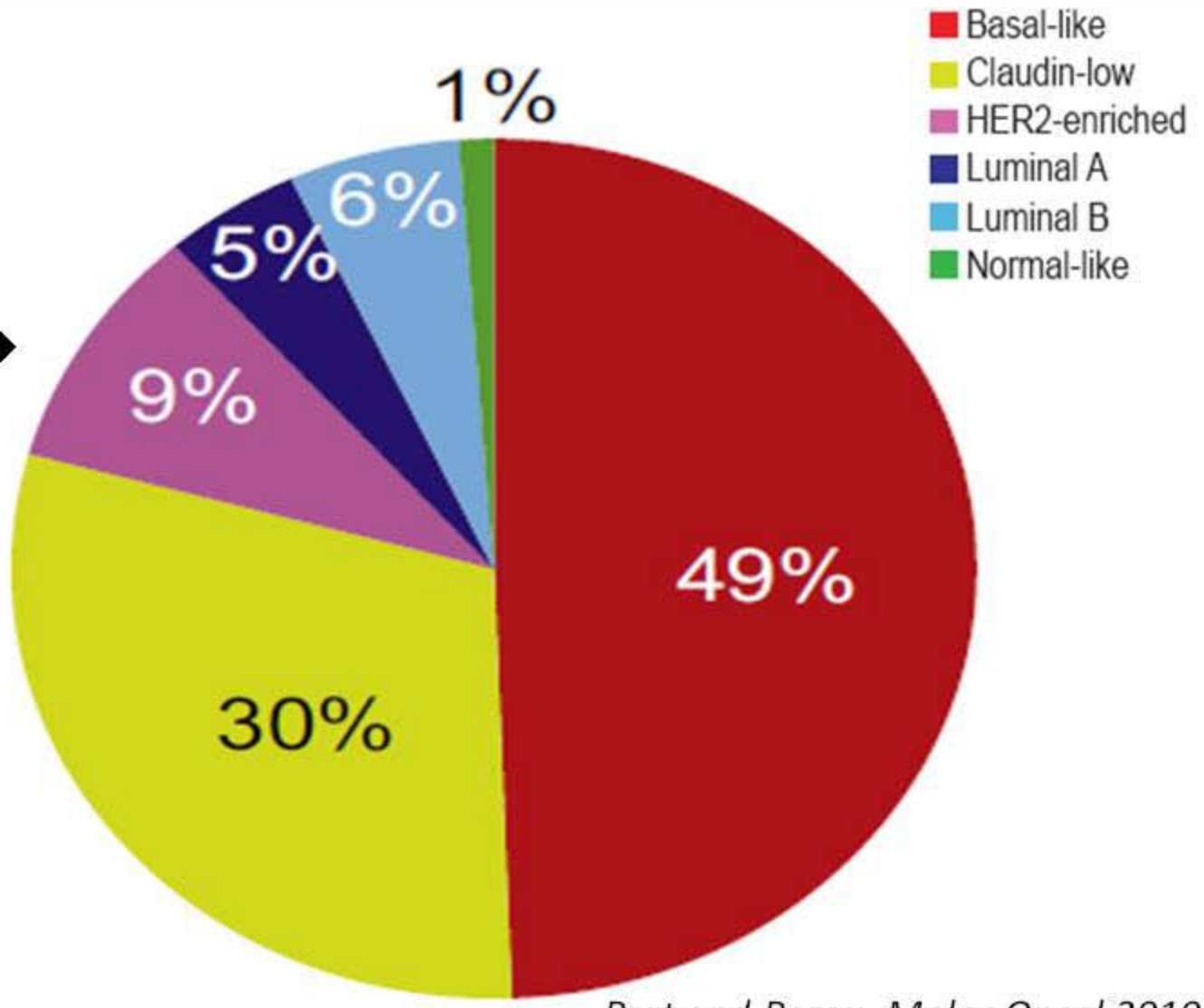
Triple Negative Breast Cancer: What Is It?

Defined by clinical assays:

- **ER- PR- HER2-**

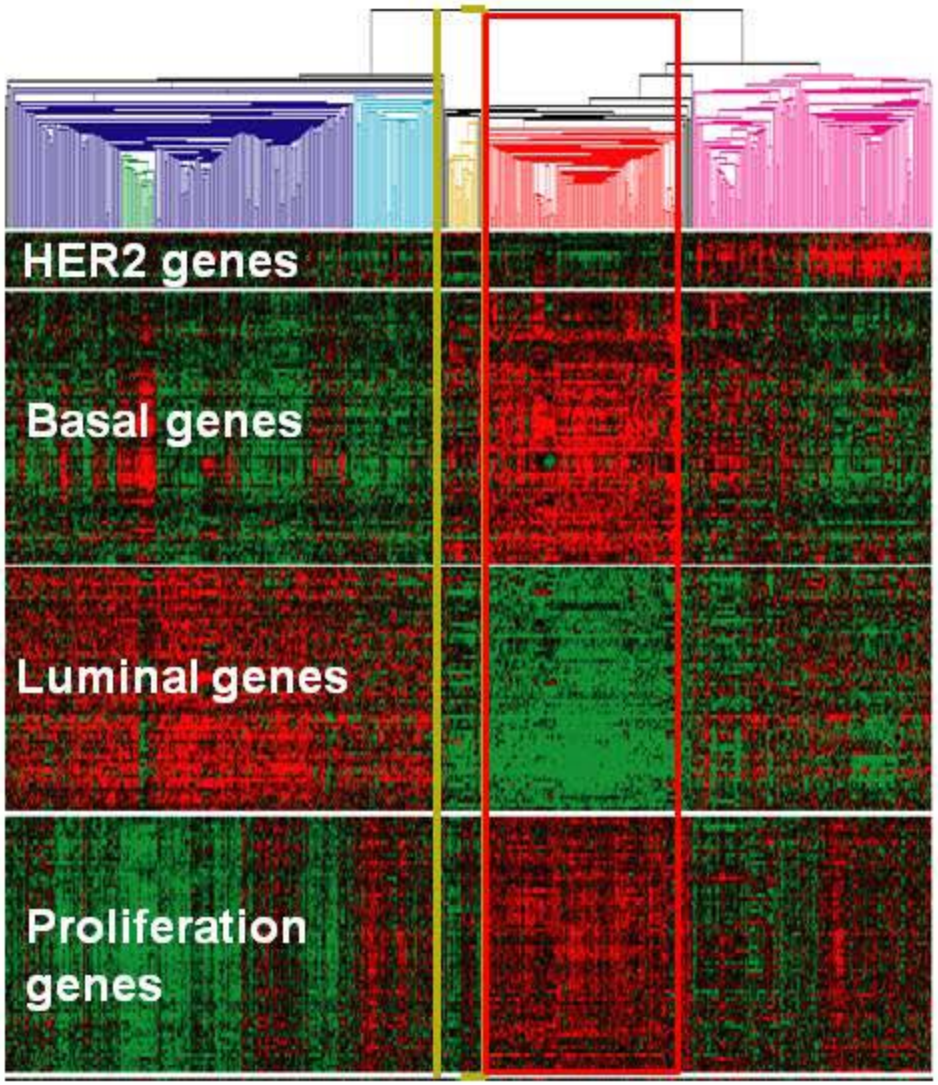
Molecular assays: ➔

- **3/4 molecularly "appropriate"**
- **1/4 are not what they seem**



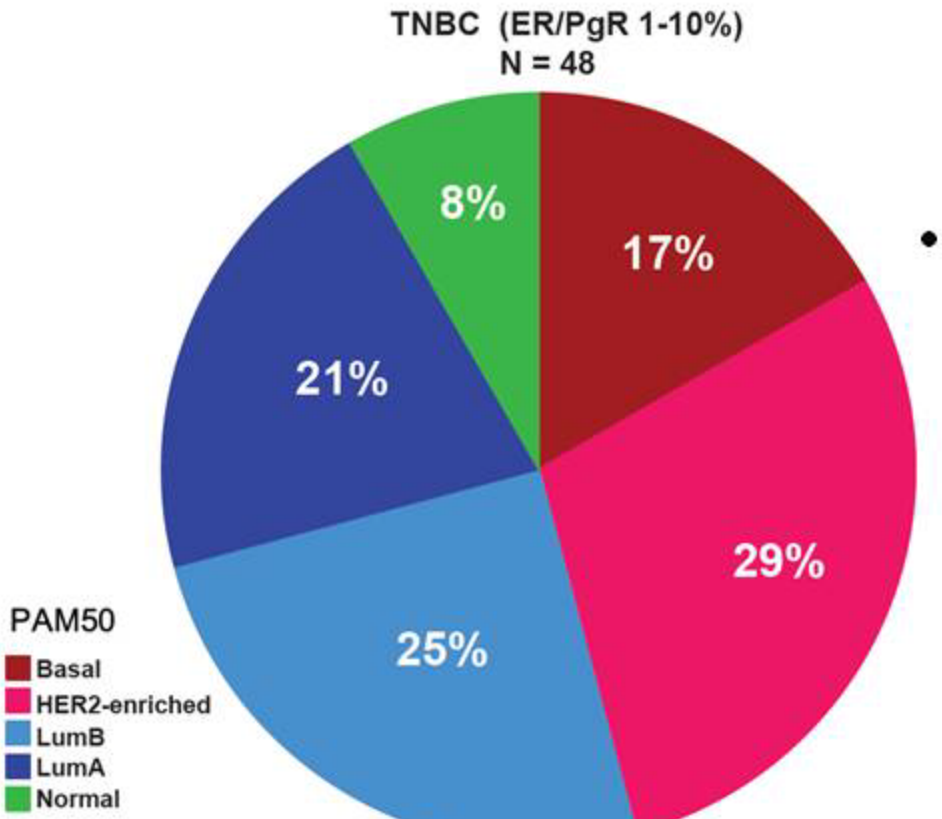
Prat and Perou, Molec Oncol 2010

Triple Negative Breast Cancer



- Basal-like molecular subtype (red)
  - Majority
  - Low HR, HER2 genes
  - High proliferation genes
  - Genomic instability
- Claudin-low (yellow)
  - Minority
  - Low HR, HER2 genes
  - Relatively low proliferation genes
  - Genetically more stable

What Are Borderline Tumors? (NCI / BIG Collaboration)

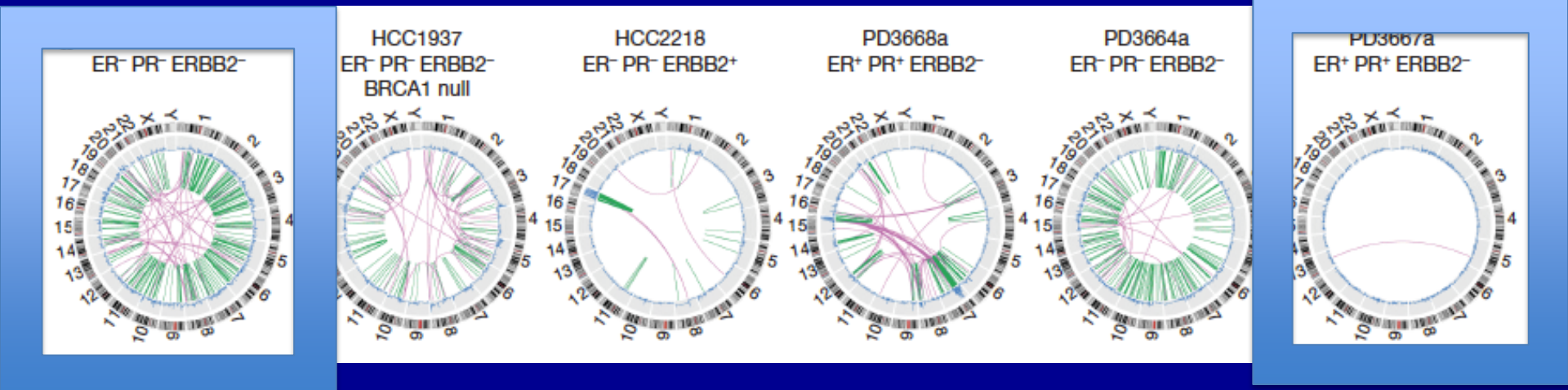


- **Borderline ER or PR (1-10%), HER2-negative:**
  - 46% Luminal
  - 17% Basal-like
  - 29% HER2-enriched

No assumptions.
Use endocrine therapy.

Cheang M et al, ASCO 2012

Breast Cancer: Subtypes Reflect Intertumor Genomic Complexity



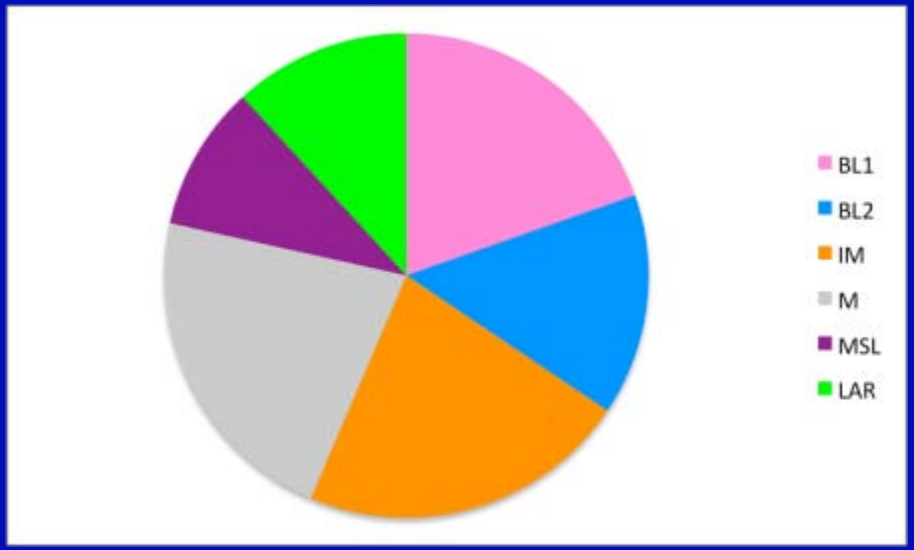
Genome-wide Circos plots
of somatic rearrangements

Stephens, PJ et al. Nature 462:1005-12, 2009.

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
- Identified breast cancer cell lines representative of each subtype

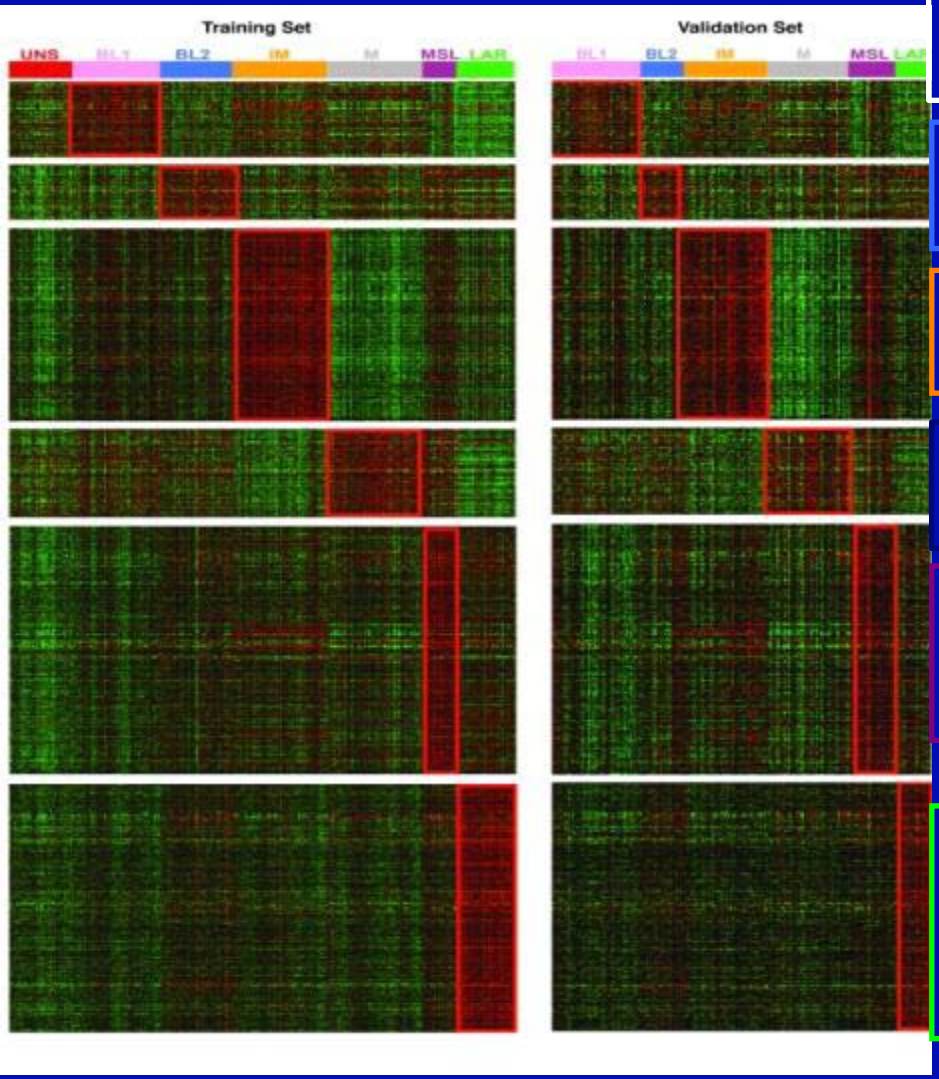
Six TNBC Subtypes



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 & cytokine signaling (overlap with medullary signature)

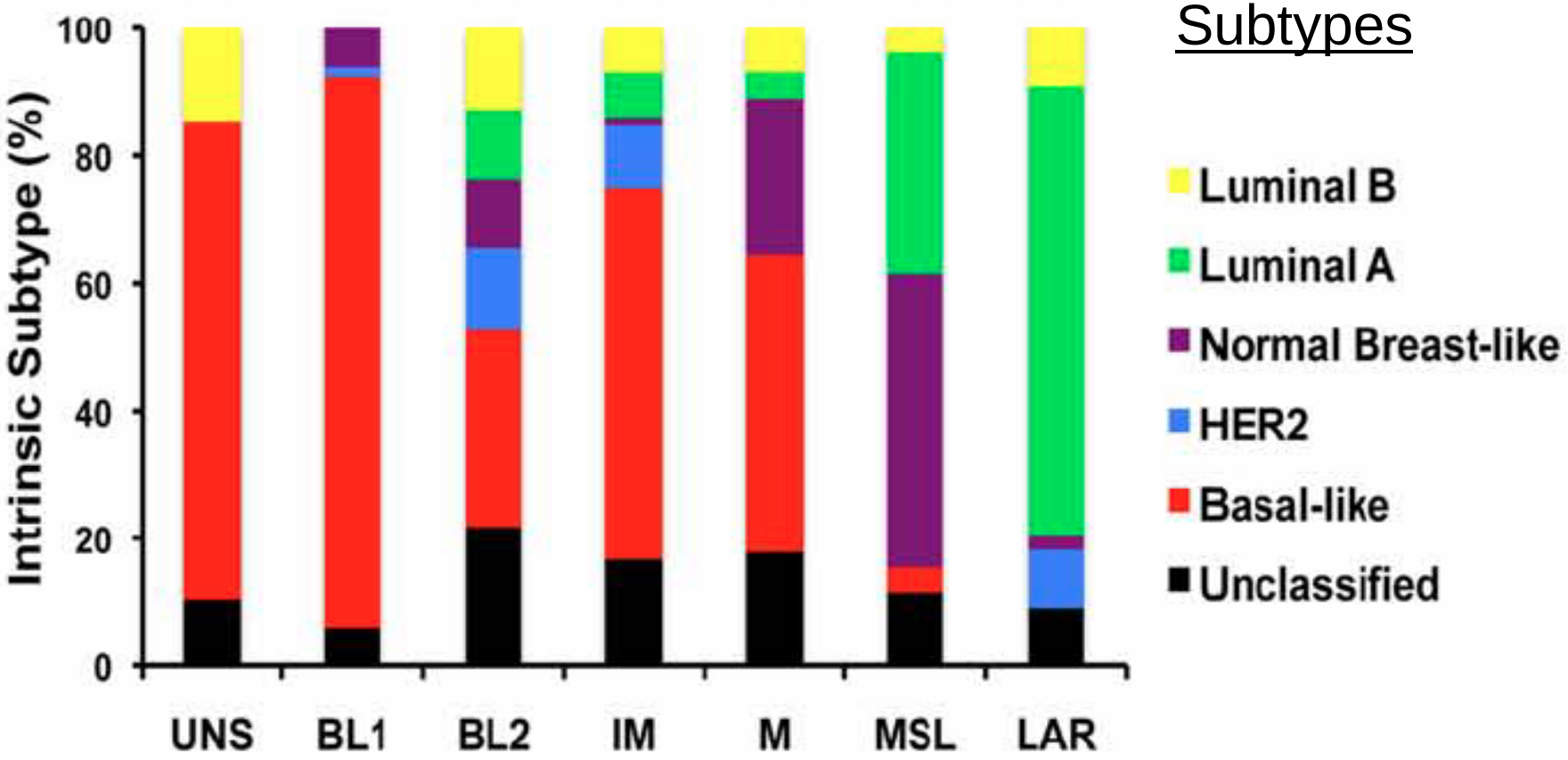
Mesenchymal (M): Cell motility and differentiation (Wnt, ALK, TGF-β)

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

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

Intrinsic subtype distribution among Vanderbilt TNBC subtypes



TNBC and Treatment: What Do We Know?

- Prognosis can be accurately estimated by the usual variables.
- Chemotherapy is the only known therapy.

Everything else is theory.

Prognosis in TNBC

T3N1 TNBC

85% 10-year risk of relapse

↓

79% 10-year risk of death

↓

(-24% = benefit of 3rd generation chemotherapy)

↓

55% 10-year risk of death

From www.adjuvantonline.com

AdjuvantOnLine and TNBC

T1aN0 TNBC

Shared Decision Making

Name: _____ (Breast Cancer)

Age: 50 General Health: Excellent

Estrogen Receptor Status: Negative Histologic Grade: 2

Tumor Size: 0.1 - 1.0 cm Nodes Involved: 0

Chemotherapy Regimen: Third Generation Regimen

Decision: No Additional Therapy

79 out of 100 women are alive and without cancer in 10 years.

19 out of 100 women relapse.

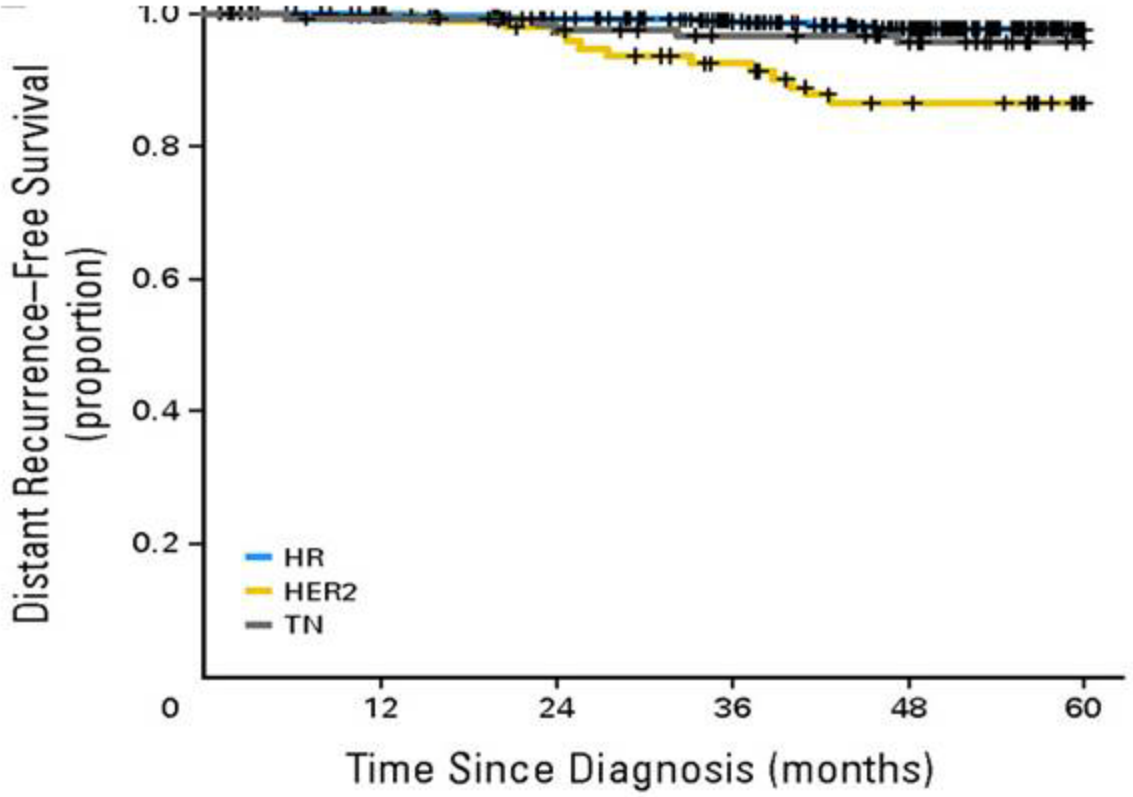
2 out of 100 women die of other causes.

- **19% relapse at 10 years**
- **8% death**

"Relapse" includes in-breast and local recurrence, new primaries and true relapse.

In TNBC, 10-year mortality may be better metric for decision-making

There Are Good Prognosis TNBC



Gonzalez-Angulo et al, JCO 2009

←

T1a-bN0, untreated
Distant RFS at 5 y

Ok to <u>not</u> treat small, node negative TNBC.

Molecular Subtypes and Standard Chemotherapy

Classification	Residual disease	pCR
Basal-like	47 (58%)	34 (42%)
Claudin-low	29 (67%)	14 (33%)
HER2-enriched	31 (63%)	18 (37%)
LumA	110 (98%)	2 (2%)
LumB	56 (85%)	10 (15%)
Normal-like	13 (76%)	4 (24%)

- 360 patients
- Anthracycline/taxane-treated
- Overall pathologic complete response (pCR) rate = 22%
- Modified PAM50 molecular subtyping

Adapted from Cheang, SABCS 2011

Take Home:

1. *Basal-like and Claudin-Low (majority of TNBC) are sensitive to conventional agents.*
2. *In (neo)adjuvant studies, underlying population is key to interpreting results.*

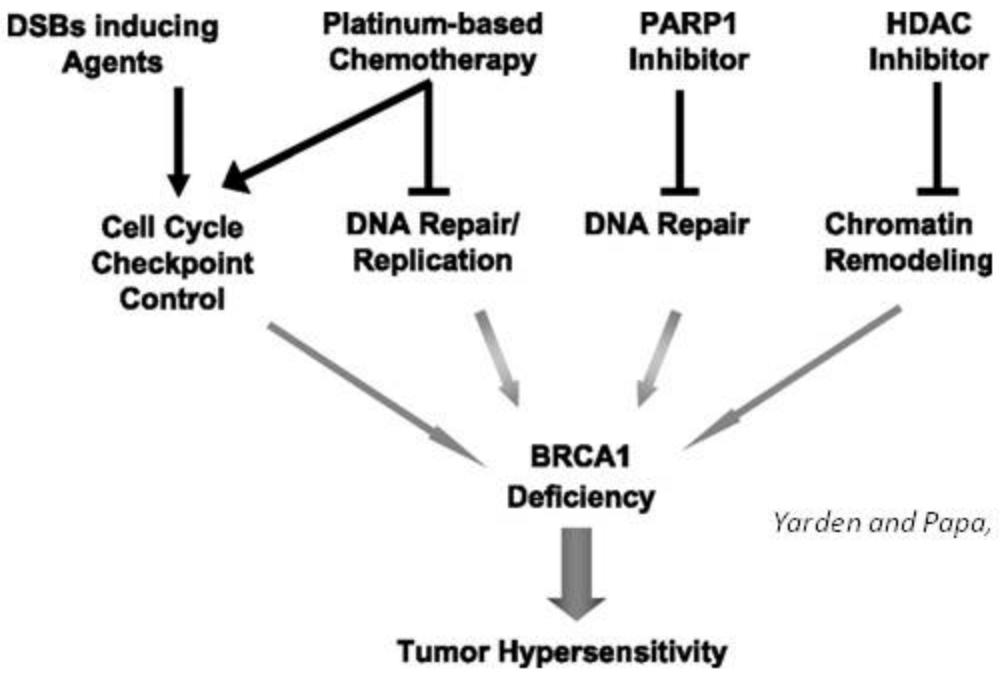
Now for the Theory Part: BRCA1-Associated Breast Cancer

- 80% of BRCA1-associated breast cancers are basal-like.
- "BRCAness" = shared characteristics with sporadic basal-like.
- If there are therapeutic implications of BRCA1 loss, does this include sporadic basal-like?

"BRCAness"

- High grade
- ER- and HER2-negative
- C-myc amplified
- Medullary
- Pushing margins
- DCIS less common
- Lymphocytic infiltrate
- TP53 mutations
- Basal phenotype
- EGFR expression
- X-chromosome inactivation pattern
- Sensitivity to DNA damage
- Aneuploidy

Theory #1: BRCA1 Loss is Targetable



Yarden and Papa, Mol Cell Ther 2006

#1 – Chemotherapy choices:

- Platinum agents damage DNA.
- *Evidence:*
  - Neoadjuvant pCR to cisplatin in known BRCA1+ = 83%

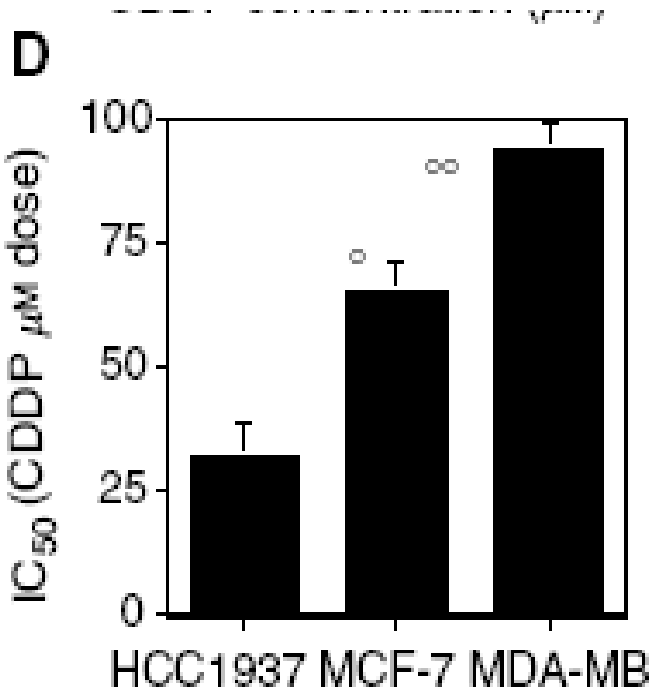
Byrski, JCO 2010

#2 – Exploiting DNA damage response:

- When DNA repair is already impaired, this is an opportunity…PARP inhibition

BRCA1-Deficient Cells are Hypersensitive to Cisplatin

- **BRCA1 deficient cells have defect in DNA DS repair**
- **BRCA1 deficient cells were more sensitive to cisplatin compared to other cell lines**
- **BRCA1 loss increases sensitivity to DNA damaging agents like cisplatin**

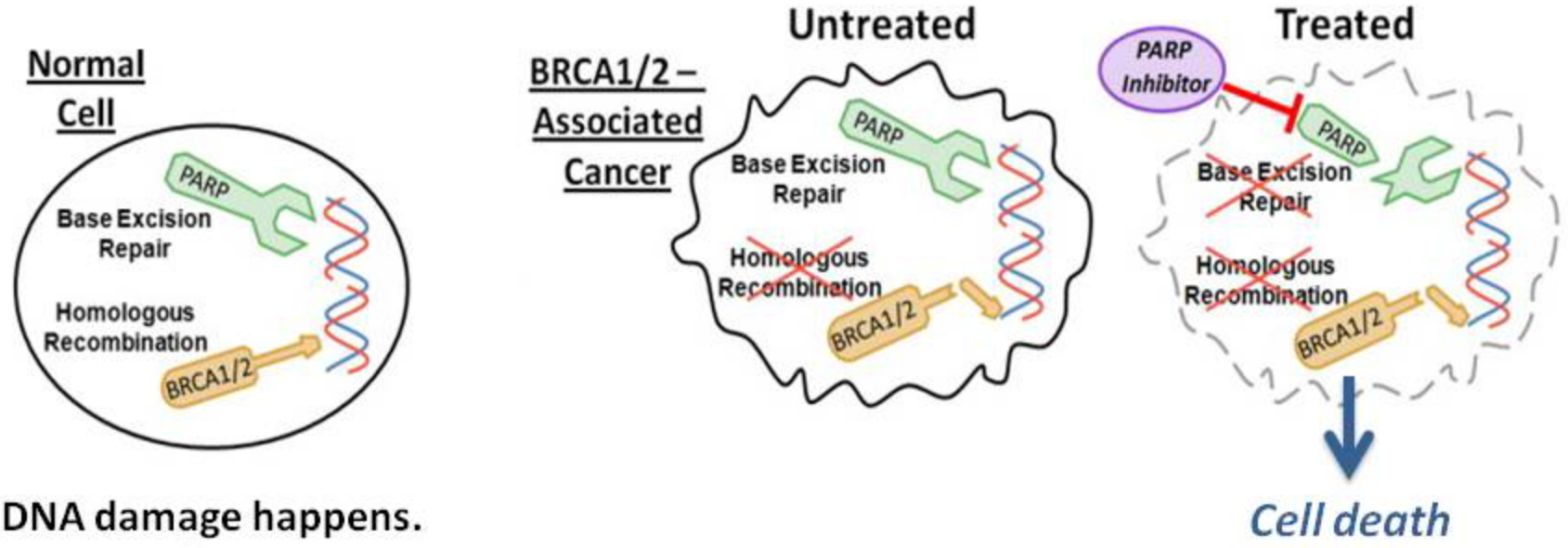


HCC1937, BRCA-deficient cell line

MCF-7, hormone-sensitive

MDA-MB230, hormone-insensitive

PARP Inhibition



DNA damage happens.

- Naturally occurring
- Induced e.g. chemo, radiation

Several repair options:

- BRCA1/2 dependent
- PARP dependent

When BRCA1 or 2 is already damaged; cell becomes dependent on other repair types.

PARP inhibitors exploit this Achilles' heel.

Phase II olaparib in 27 BRCA+

- 67% BRCA1 (50% TNBC)
- Heavily pretreated

= 41% RR of a single agent

Ellisen, Cancer Cell 2011; Tutt et al, Lancet 2010

pCR in BRCA1-Associated Breast Cancer Receiving Neoadjuvant Chemotherapy

J Clin Oncol. 2010; 28:375-9. Epub 2009 Dec 14.

- **Registry of 6,903 patients**
- **102 BRCA1 founder mutation and received neoadjuvant chemotherapy**
- **24 (24%) has a pCR**
  - **CMF: 1 of 14 (7%)**
  - **AT (docetaxel): 2 of 25 (8%)**
  - **AC of FAC: 11 of 51 (22%)**
  - **Cisplatin: 10 of 12 (83%)**

Non-BRCA1 TNBC and Platinums?

Stage IV Trials	Population	Results
Control arm BALI-1 (CDDP)	Sporadic TNBC	10% RR
Control arm Phase III iniparib (Gem/carbo)	Sporadic TNBC	30% RR
TBCRC 001 (Cetuximab/Carbo)	Sporadic TNBC	17% RR
TBCRC 009 (Carboplatin or Cisplatin)	Sporadic TNBC	30% RR

Platinums and DNA-damaging chemotherapy:

- *Promising in BRCA-associated*
- *Unclear in sporadic TNBC*

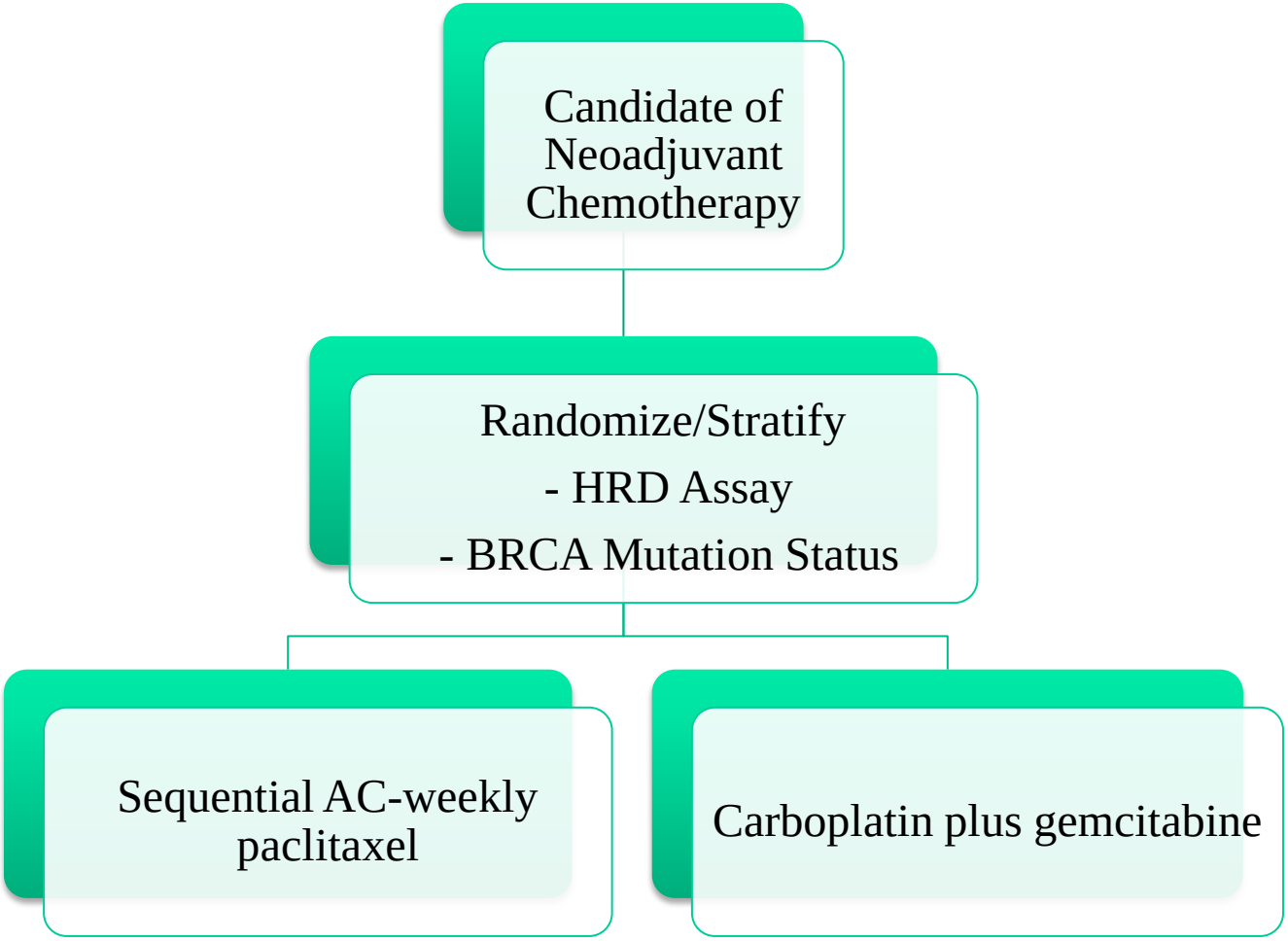
Baselga, ESMO'10; O'Shaughnessy, ASCO'11; Carey et al, JCO'12; Isakoff, ASCO'11

Breast pCR Rates after Single Agent Cytotoxic Neoadjuvant Therapy in Triple Negative Disease

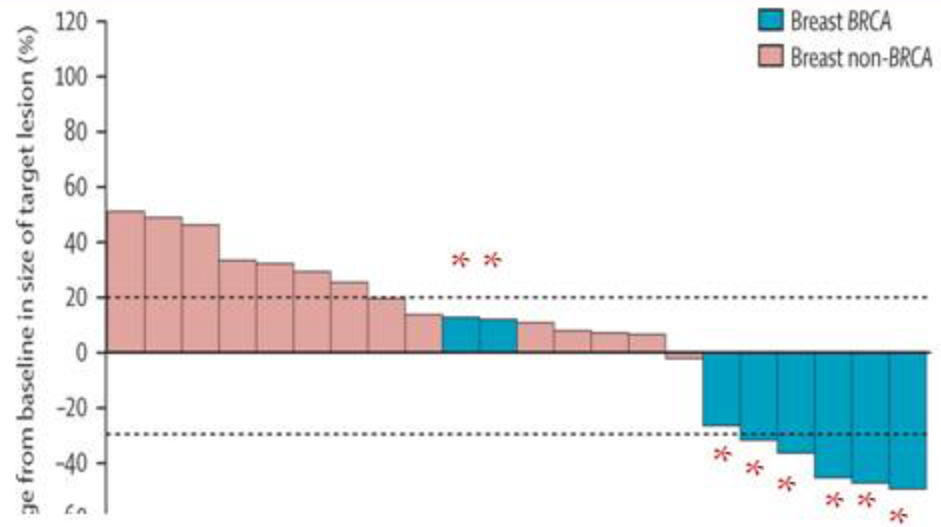
Reference	**Agent**	**No.**	**pCR**
Garber et al. JCO 2009	Cisplatin 75 mg/m2 q 3 wks x 4	22	5 (22%)
Baselga JCO 2009	Ixabepilone 100 mg/m2 q3 wks x 4	42	11 (26%)
Martin ASCO 2010	Doxorubicin 75 mg/m2 q 3wks x 4	20	2 (10%)
	Docetaxel 100 mg/m2 q 3 wks x 4	28	8 (27%)

Proposed Phase II-III ECOG Neoadjuvant Trial in TNBC

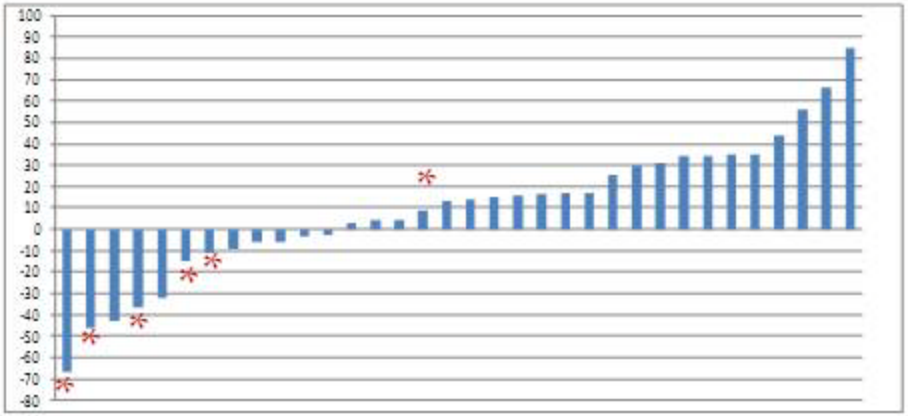
Study Chair: Melinda Telli, MD



PARP Inhibition in TNBC



* BRCA1/2-associated



Phase II olaparib in BRCA+ and TNBC:

PARP Inhibition

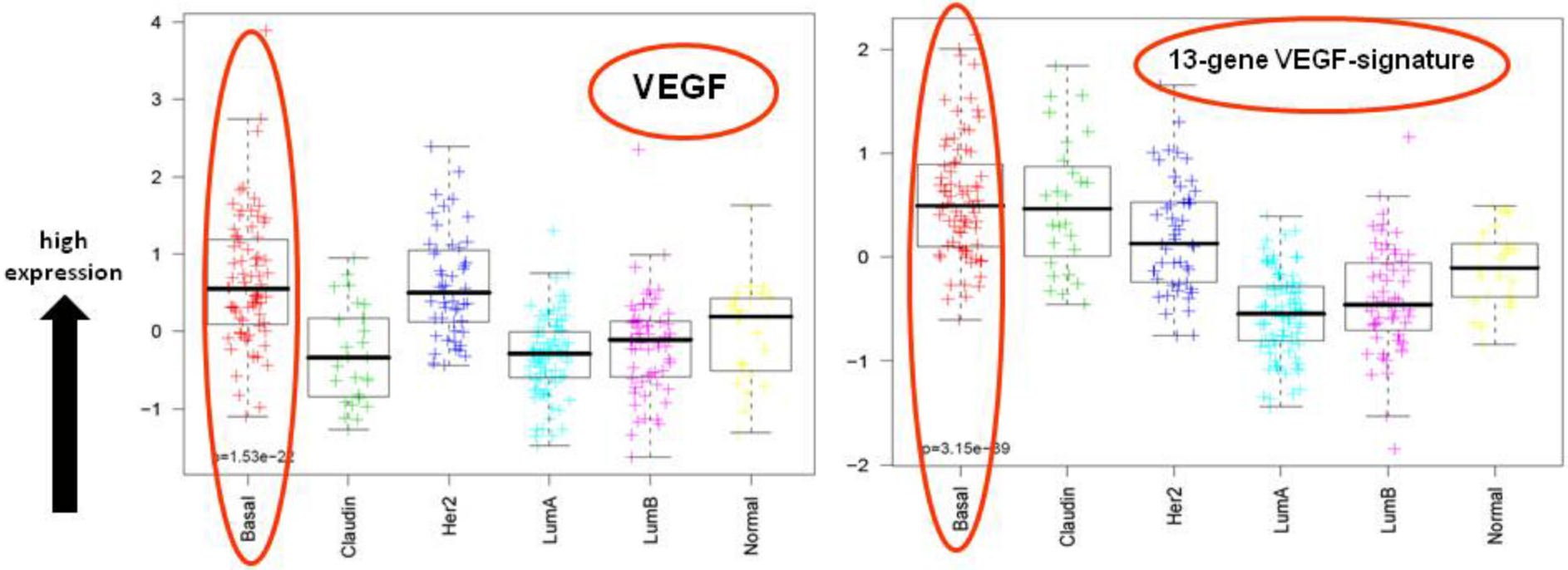
- ***Promising in BRCA-associated***
- ***Unclear in sporadic TNBC***

Phase II veliparib + temozolamide:

Gelmon et al, Lancet Oncol 2011; Isakoff et al, ASCO 2011

Theory #2: Antiangiogenic Drugs

Preclinical data suggests that TNBC may be particularly susceptible to antiangiogenic approaches …



Hu et al, BMC Medicine 2009

Biological Agents

Reality?
Bevacizumab in TNBC

First-line stage IV trials:

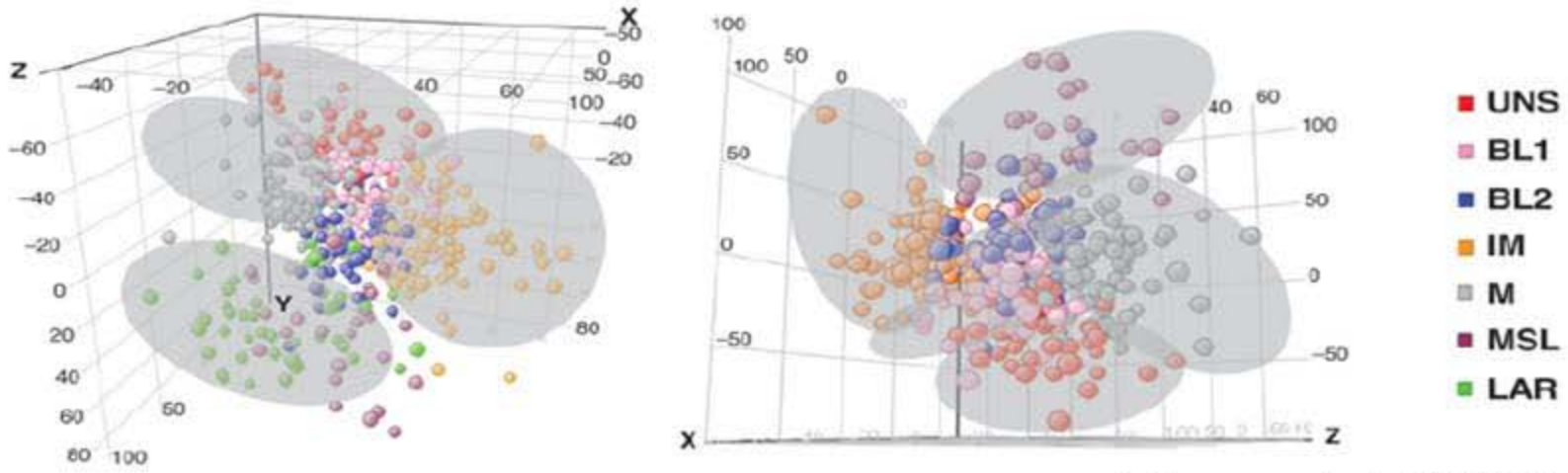
Trial	Regimen	PFS HR (95% CI)
ECOG 2100	Paclitaxel ± bevacizumab	0.53 (0.41-0.70)
AVADO	Docetaxel ± bevacizumab	0.68 (NR~1.00)
RIBBON-1	Chemotherapy ± bevacizumab	0.72 (0.49-1.06
Meta-analysis chemo ± bevacizumab		OS HR = 0.96 (0.79-1.16)

Neoadjuvant trials:

Trial	Regimen	pCR HR (95% CI)
GeparQuinto	EC-docetaxel ± bevacizumab	1.67 (*) *(1.00 in HR+ subset)*
NSABP B-40	chemo ± bevacizumab	<1.2 (ns) *(*significant in HR+ subset)*

O'Shaughnessy, ASCO'11; Von Minckwitz, NEJM'12; Bear, NEJM'12

Theory #3: Targeting Heterogeneity of TNBC

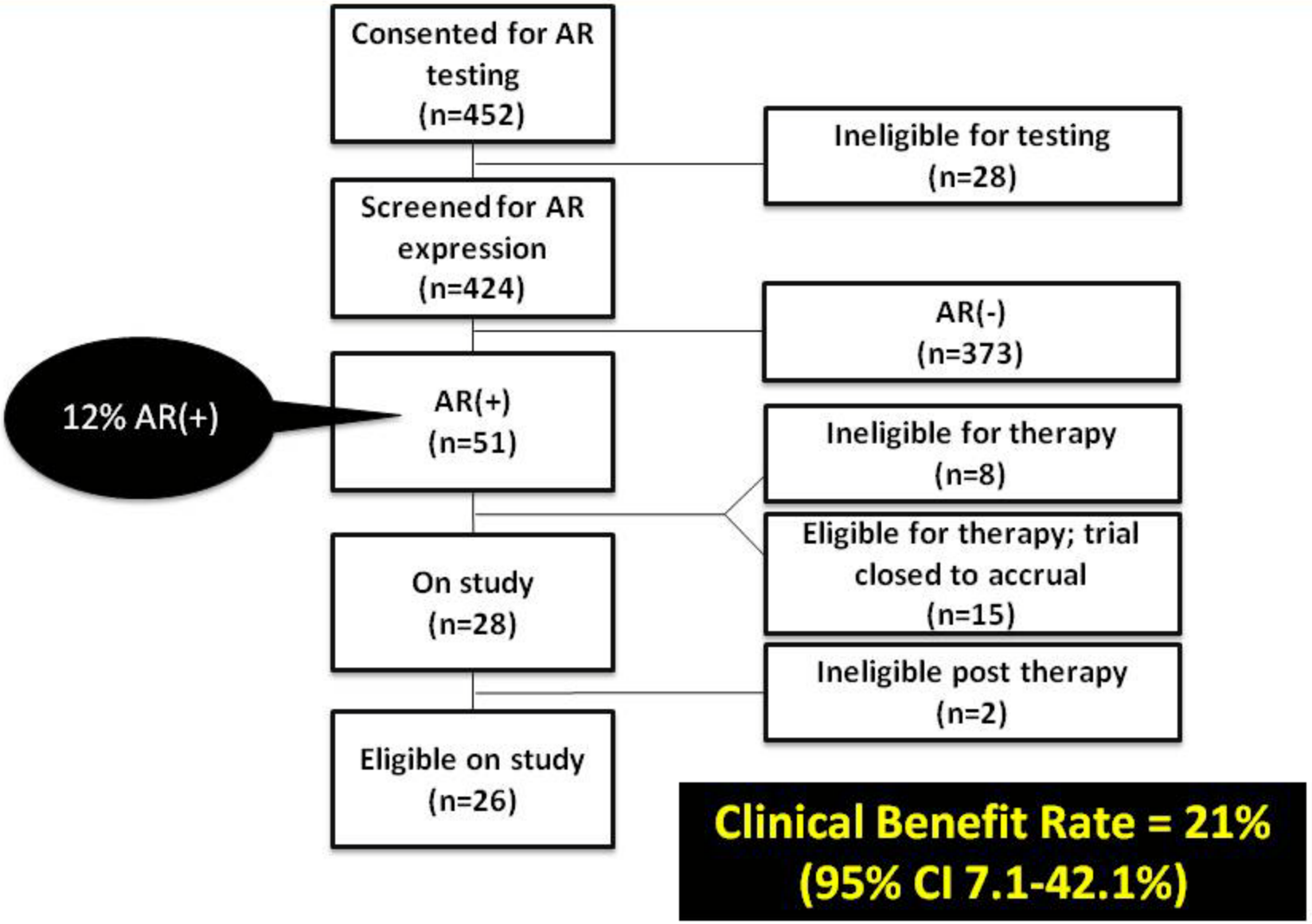


Lehmann et al, JCI 2011

Multiple potential targets?

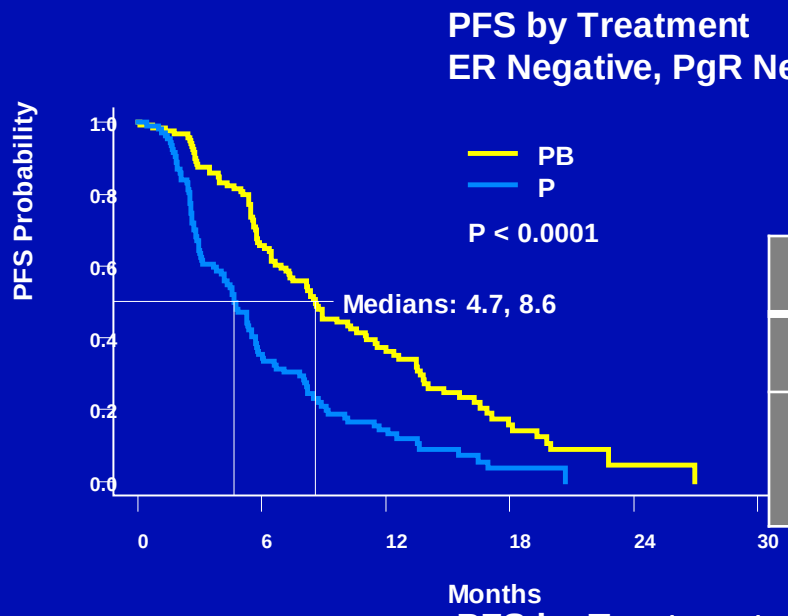
- **Basal-like 1 and 2 – DNA damage response genes, growth factor paths (EGFR)**
- **Immunomodulatory - ? Immune approaches**
- **Mesenchymal and mesenchymal / stem cell – PI3K/mTOR pathway**
- **LAR – androgen receptor signaling**

TBCRC 011: Bicalutamide in AR+ TNBC



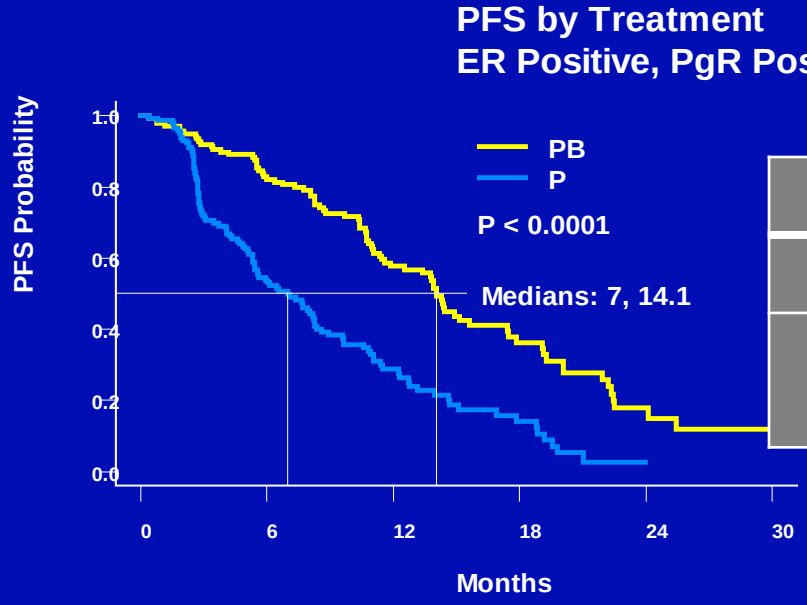
Gucalp et al, ASCO 2012

E2100: Weekly paclitaxel alone or plus bevacizumab as first-line therapy for metastatic breast cancer – outcomes by ER/PR expression



ER/PR Negative

	P	P+B
All	17%	34%
Measurable (79%)	17%	41%



ER and/or PR Positive

	P	P+B
All	23%	37%
Measurable (46%)	30%	51%

Targeting EGFR
BALI-1

Rationale: EGFR part of "basal" gene cluster, basal-like preclinical models depend on EGFR

Stage IV triple negative breast cancer

randomize

	Cisplatin	Cisplatinum + Cetuximab
CR	**1.7%**	**1.7%**
PR	**8.6%**	**18.3%**
ORR	**10.3%** [3.9-21.2%]	**20.0%** [13.1-28.%]
PFS (clinical)	**1.5 mos**	**3.1 mos**
PFS (radiographic)	**1.5 mos**	**3.7 mos**

Baselga, ESMO 2010

Some improvement but not enough.
Needs selection strategy.

Randomized Trials of Cetuximab in Triple Negative Metastatic Breast Cancer

Author	No.	Treatment Arms	ORR	Median PFS
Carey et al TBCRC001	102	Cetuximab ➔ Cet/carbo Carboplatin + cetuximab	6% 17%	1.4 mo. 2.1 mo.
Baselga et al BALI-1	173	Cisplatin Cisplatin + cetuximab	10% 20%	1.5 mo. 3.7 mo. (p=0.03)
O'Shaugnessy et al	154	Irinotecan + carbo ➔cetuximab Irinotecan + carbo + cetuximab	28% 33%	4.5 mo. 4.7 mo.

Carey et al. J Clin Onc 2012; 30: 2615-2623
Baselga et al. *Proc SABCS* 2010;Abstract PD01-01
O'Shaughnessy et al. Proc SABCS 2008; Abstract 308.

Summary

What we know:

- **TNBC is heterogeneous**
- **Adjuvant chemotherapy is the same as for other subtypes**

What we'd like to know:

- **Identifying BRCA-like tumors**
- **Is TNBC where individualized therapy will start?**

Alignment of tissue-based and clinical trials is key