What's Positive about Triple Negative Breast Cancer?

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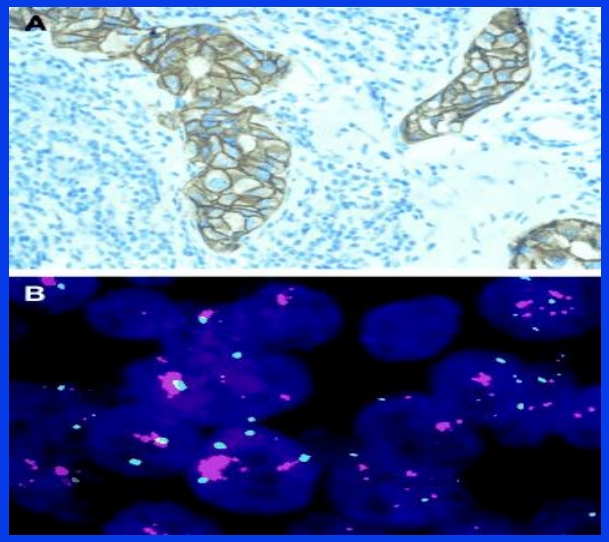
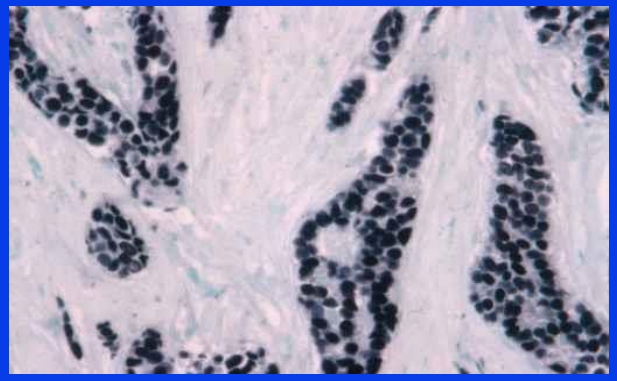
Breast Cancer: Classic Prognostic and Predictive Factors



HER-2 +
20-25% of
Breast Cancer



Estrogen
Receptor (ER) +
75% of Breast
Cancer

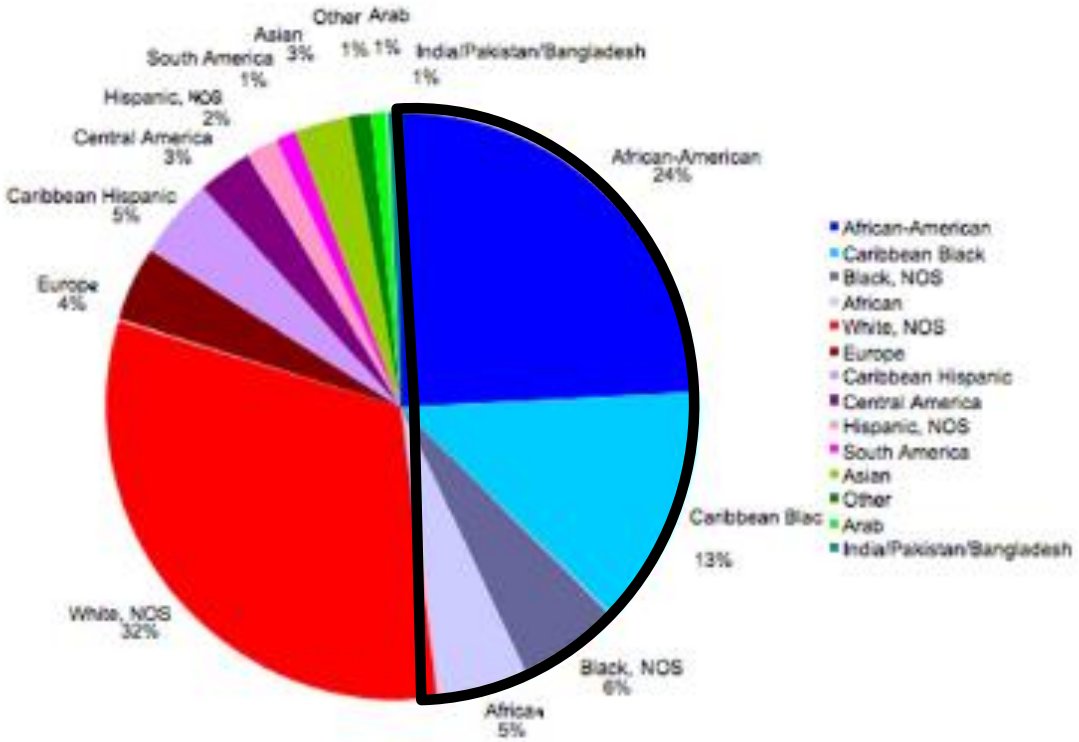
Triple Negative Breast Cancer

- No expression of ER, PR, ER2
- 15% of breast cancers
- Aggressive, higher recurrence rates
- Chemotherapy is currently main treatment option
- More common in:
  - Young women
  - African Americans
  - Hispanics
  - BRCA1+ (80%)

Racial Distribution of Triple Negative Breast Cancer

Stead LA, et al, Breast Cancer Research 11:R18, 2009

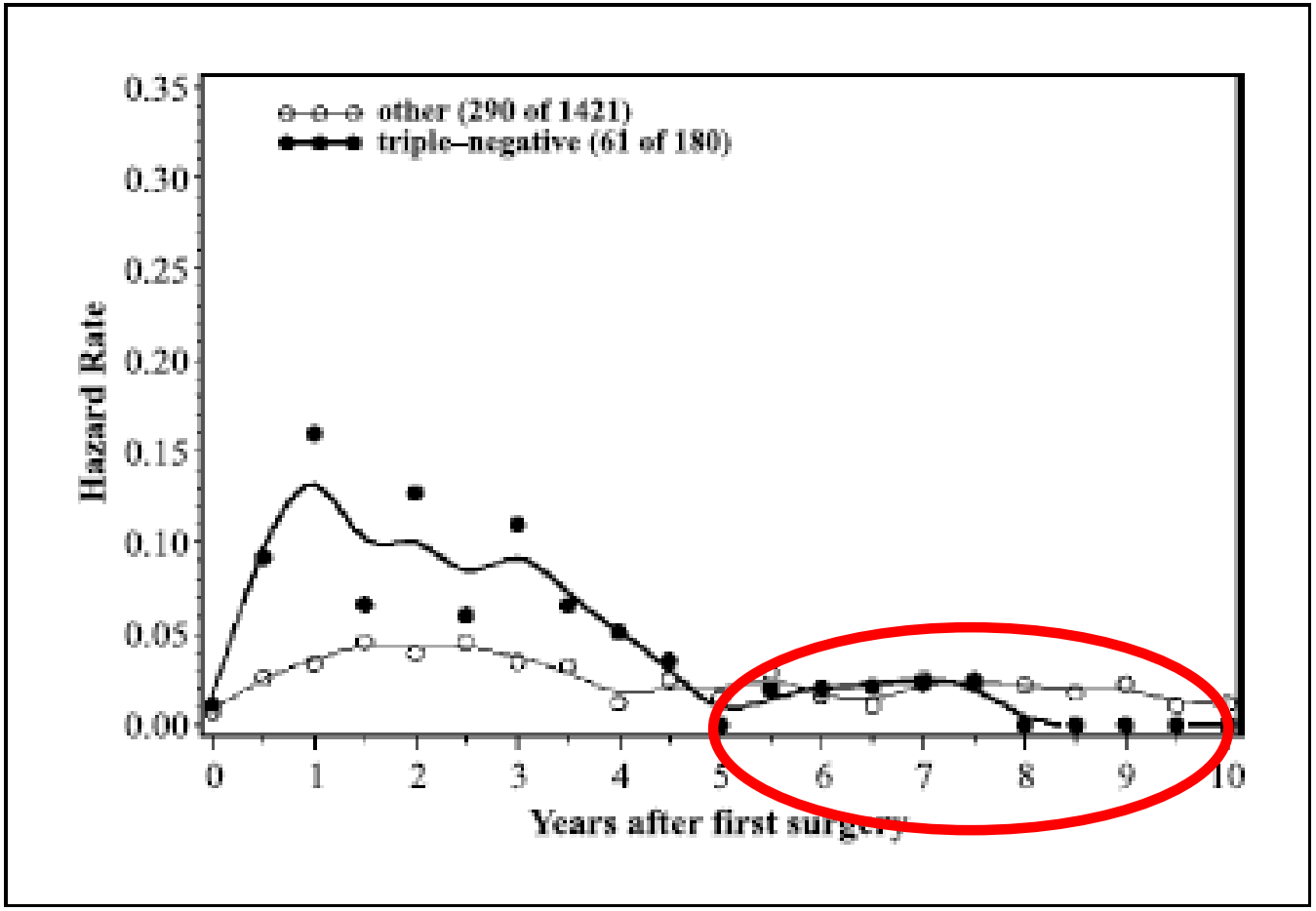
Figure 1



Distribution of breast cancer patients by race/ethnicity. The chart depicts the proportion of patients by race/ethnicity, classifying them by region of origin. NOS, not otherwise specified.

Timing of Recurrence in Triple Negative Breast Cancer vs. Other Subtypes

Dent et al. Clin Can Res 2007; 13: 4429



Gene Expression Profiling in Breast Cancer

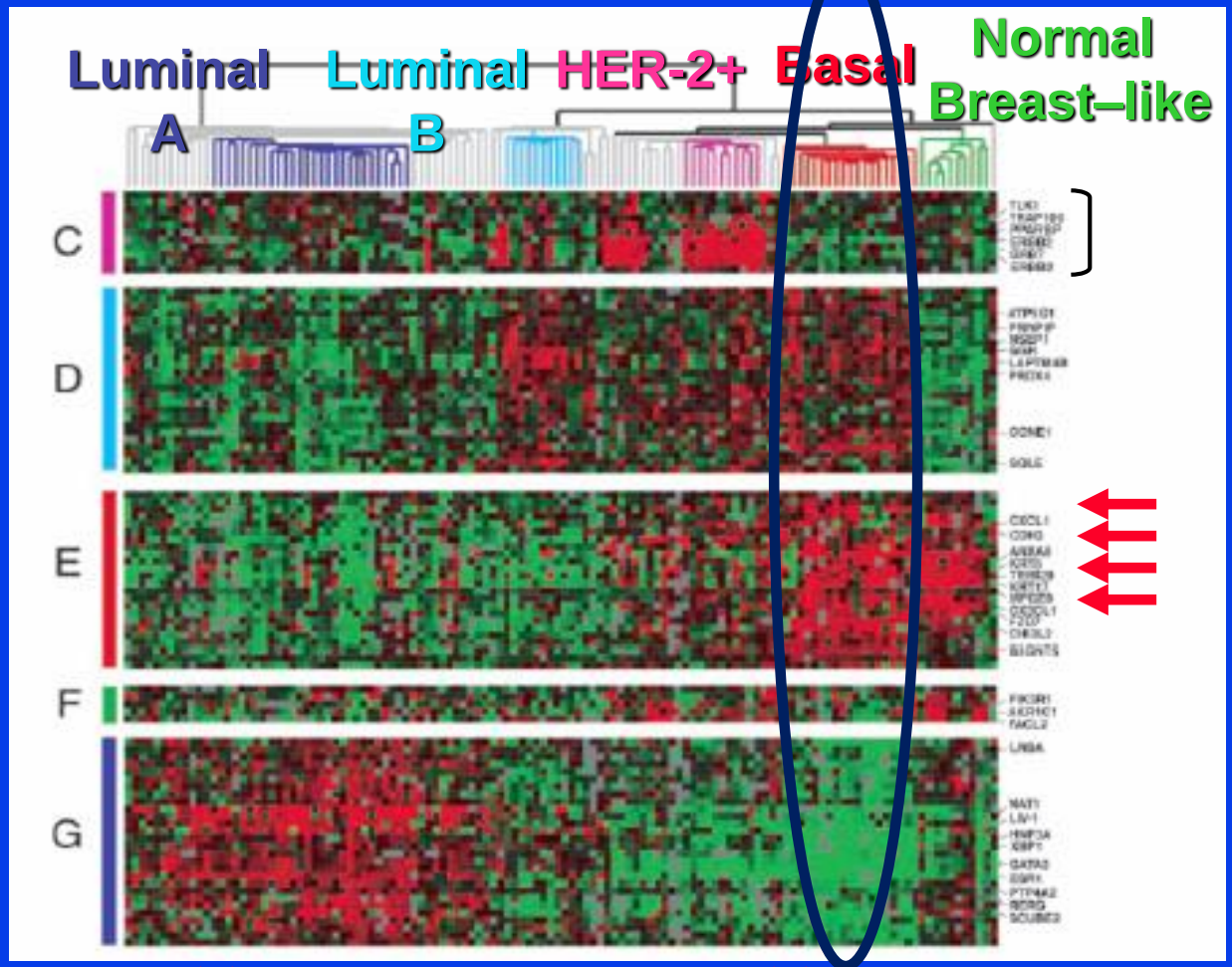
- Over the last decade, gene expression profiling has given us insights into the biological complexity of breast tumors
- Clinically applicable gene expression-based assays have been and are being developed for prediction of prognosis and/or treatment benefit

Molecular Classification of Breast Cancer: Breast Cancer is NOT One Disease!

The Cancer Genome Atlas Network. Nature 490, 2012

"Heat Map"

Red dots: Genes are "turned up" in cancer cells compared to normal cells



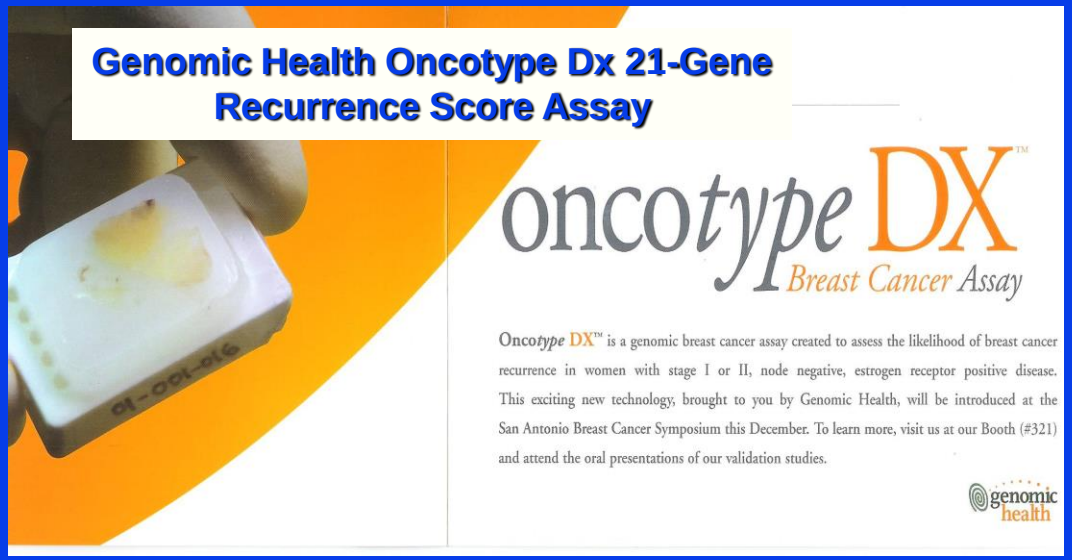
Individual genes

Individual patients

Basal Subtype

- Low expression of luminal and HER2 gene clusters
  - Typically ER-, PR-, and HER-2-negative, but up to 30 percent discordance
- High expression of proliferation cluster genes, virtually always high grade, widespread genomic instability
  - High expression of EGFR and unique basal cluster genes (basal epithelial cytokeratins 5, 14, and 17)
  - p53 mutations common
  - Other receptors and pathways can be altered (c-kit, c-met, RAS-MAPK, mTOR/PI3K)
- Strong association with cancers in BRCA1 mutation carriers (over 80 percent basal-like)
- Associated with DNA repair defects
  - PARP1 commonly increased

Clinically Available Genomic Assays in Breast Cancer



- OncotypeDX and Mammaprint provide prognostic information in early breast cancer
- OncotypeDX provides predictive information of benefit from adjuvant chemotherapy in ER-positive disease

PAM50 Breast Cancer Intrinsic Classifier Assay

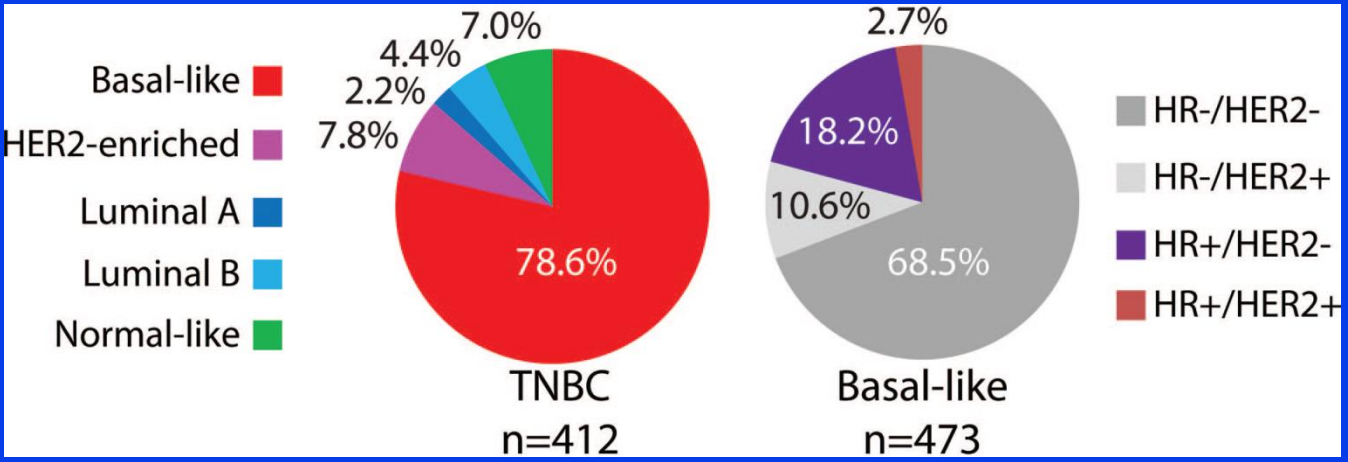
- PAM50 classifier identifies the four major biologic subtypes of breast cancer referred to as Luminal A, Luminal B, HER2-enriched, and Basal-like
- Measures 50 classifier genes and 5 control genes through RT-qPCR
- Investigational in US
- Clinical validation studies ongoing

Not all Triple Negative Breast Cancers are Basal Subtype, and Not all Basal Breast Cancers are Triple Negative

Prat A et al, Oncologist 2013 epub ahead of print

Clinical status (by standard pathology testing): Triple Negative

Subtype status (by genomic profiling): Basal



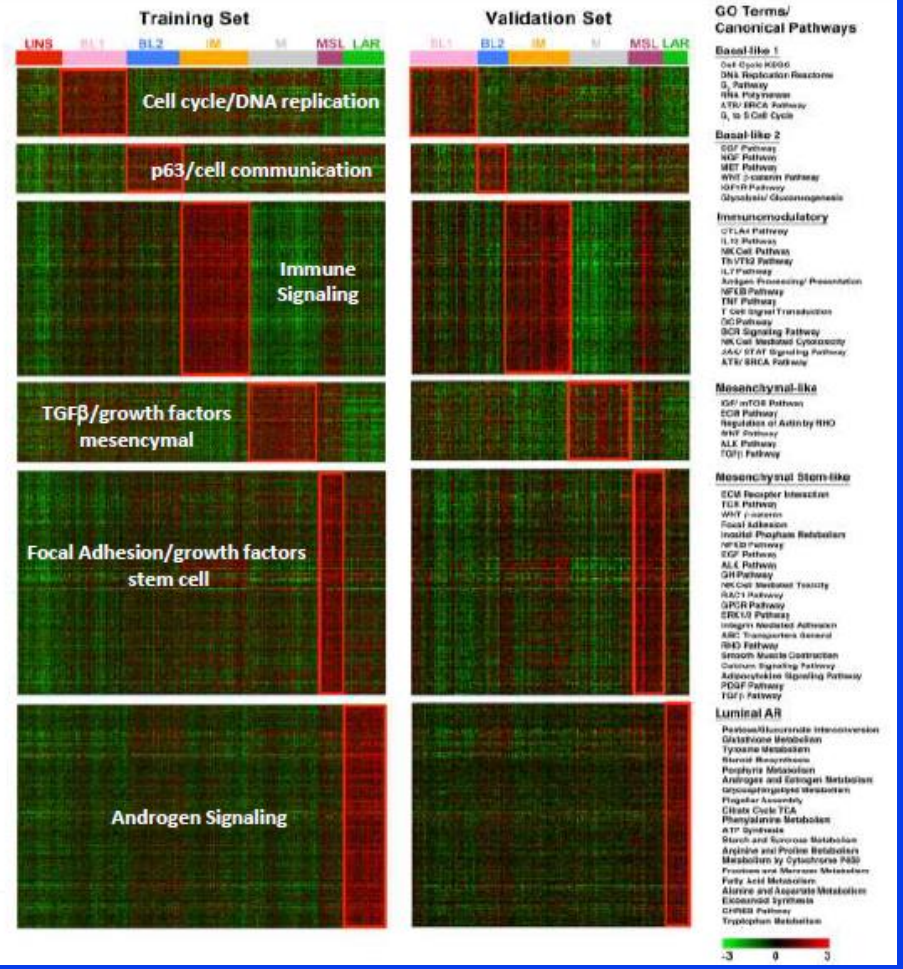
Triple Negative Breast Cancer: Subtypes and Therapeutic Targets

Lehmann B, JCI 2011; Pietenpol J. SABCS 2012

Genomic Profiling of TNBC: 6 Subtypes Identified!

Analysis of 21 public data sets
Identified 587 TNBCs
386 in training set
201 in validation set

UNS Unclassified
BL1 Basal-like 1
BL2 Basal-like 2
IM Immunomodulatory
M Mesenchymal
MSL Mesenchymal/Stem-like
LAR Luminal/Androgen receptor



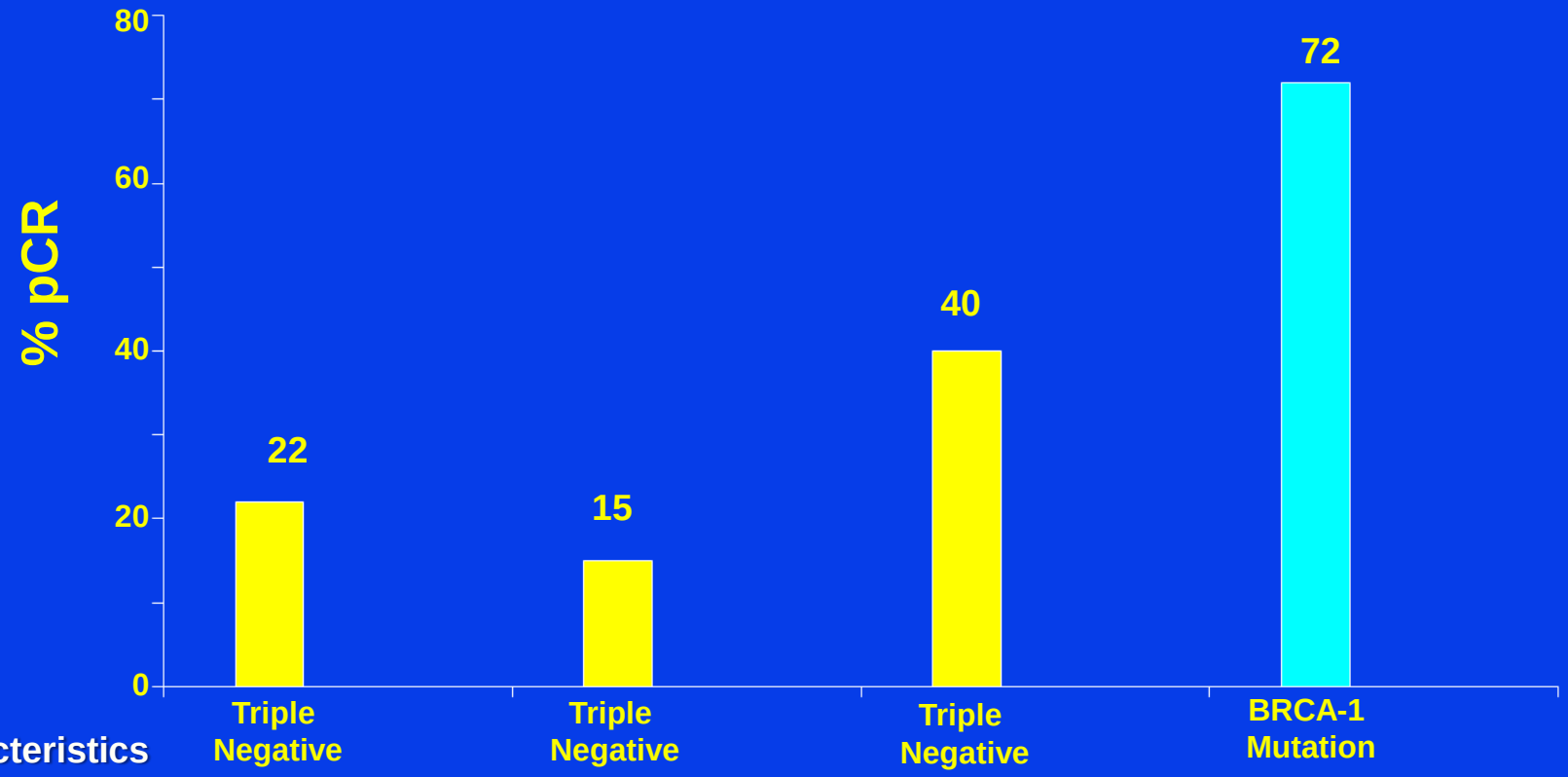
Differential sensitivity of TNBC cell lines to targeted agents due to distinct expression patterns, expression of key mutations in oncogenes and tumor suppressors

Treatment Approaches for Triple Negative Breast Cancer

- Specific chemotherapy agents (e.g. platinums)
- Anti-angiogenics (blood vessel blockers)
- Poly ADP ribose polymerase (PARP) inhibitors

Preoperative Chemotherapy with Platinum Compounds: Phase II Trials

Garber	Ryan	Torrisi	Gronwald
CDDP → Surg	CDDP/BEV → Surg	ECF → P → Surg	CDDP → Surg
N = 28	N = 51	N = 30	N = 25



1. Garber JE, et al. *Breast Cancer Res Treat.* 2006;100(Suppl 1): Abstract 3074. 2. Ryan PD, et al. *J Clin Oncol.* 2009;27(15S): Abstract 551. 3. Torrisi R, et al. *Cancer Chemother Pharmacol.* 2008;62(4):667-672. 4. Gronwald J, et al. *J Clin Oncol.* 2009;27(15S): Abstract 502.

TBCRC 009: Phase II Study of Cisplatin or Carboplatin in Metastatic TNBC

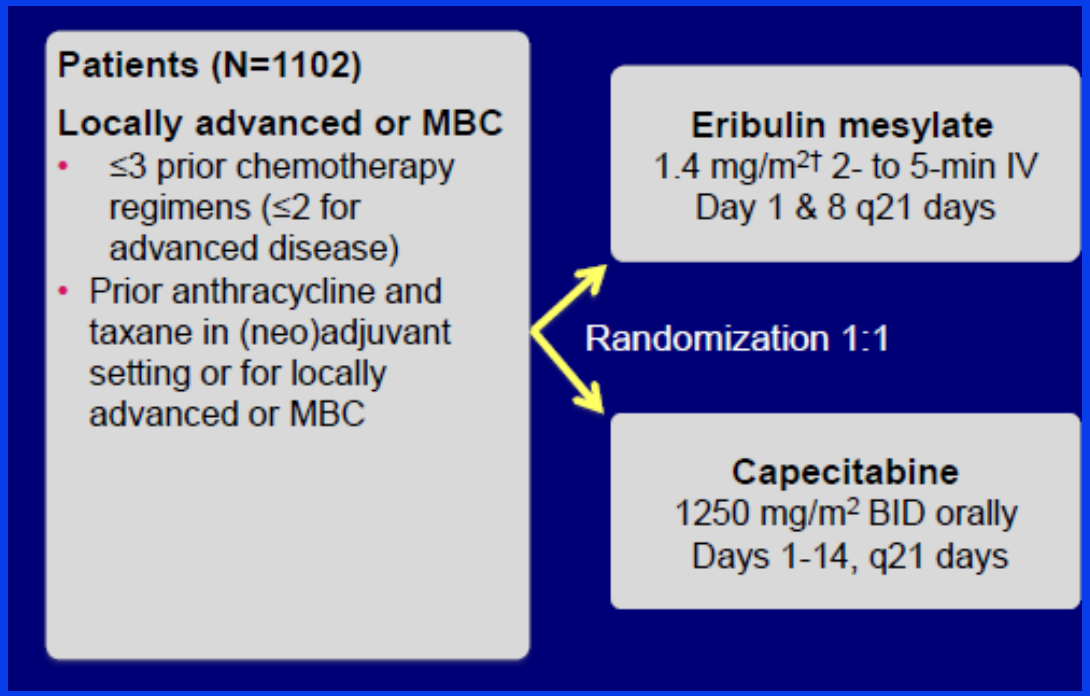
Isakoff SJ et al, ASCO 2011 abstract # 1025

- Patients: 86 metastatic TNBC
- Treatment: Randomized to cisplatin or carboplatin
- Results:
  - Response Rate 30% overall
    - » Cisplatin 37%
    - » Carboplatin 23%
  - 1st line RR 32%, 2nd line 20%
- Conclusion: Both active and well-tolerated
  - Evaluating p63/73 for prediction of response

Phase III Trial of Eribulin vs Capecitabine for Metastatic Breast Cancer

Kaufman P et al, SABCS 2012 Abstract # S6-6

- **Eribulin has demonstrated survival benefit in heavily pre-treated metastatic breast cancer**
- **Capecitabine approved for treatment of metastatic breast cancer following exposure to anthracycline/taxane**



Co-primary endpoint

- **OS and PFS**

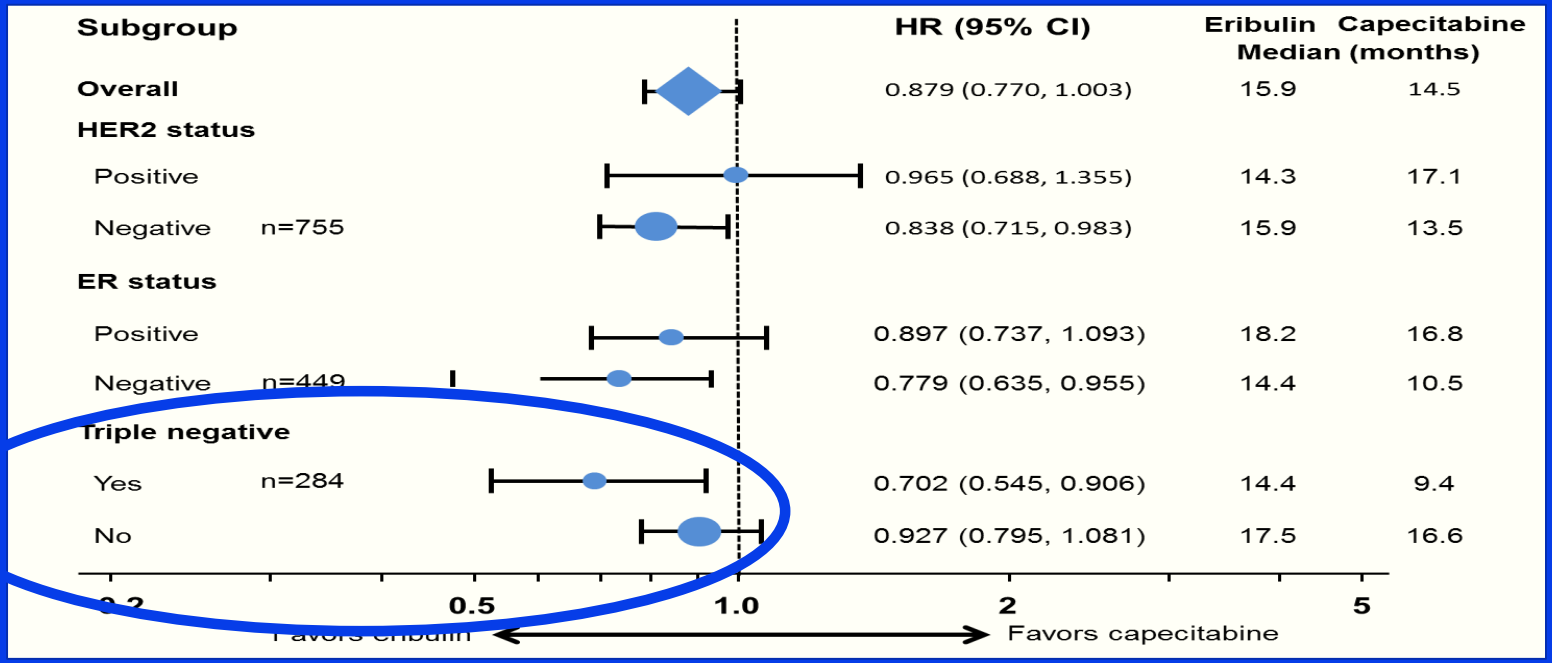
Line of therapy

- **20% 1st line**
- **50% 2nd line**
- **30% > 3rd line**

Phase III Trial of Eribulin vs Capecitabine for Metastatic Breast Cancer

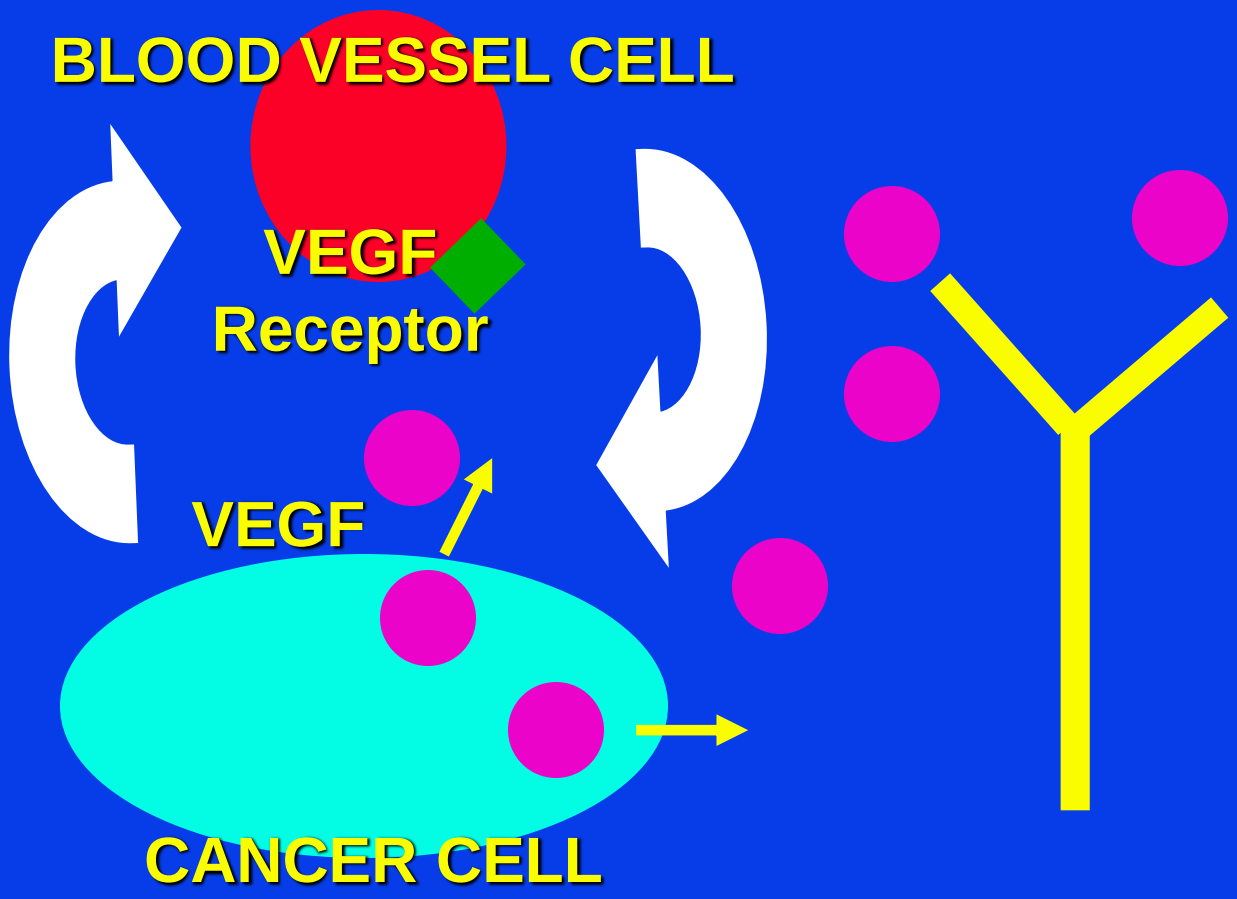
Kaufman P et al, SABCS 2012 Abstract # S6-6

Overall survival by receptor status



- No significant difference between eribulin and capecitabine
- Exploratory analysis suggests possible increased benefit for eribulin in certain subsets (ER-, TNBC)
  - TNBC: Overall survival 14.4 months eribulin, 9.4 months capecitabine

Angiogenesis Inhibition: Agents Targeting the VEGF Pathway



Bevacizumab (Avastin) Anti-VEGF Antibody: binds to VEGF and blocks tumor blood vessel growth

Other VEGF/VEGFR inhibitors:
sunitinib
sorafenib
axitinib
pazopanib

1st-Line Bevacizumab

E2100: Paclitaxel +/- Bevacizumab in Stage IV Breast Cancer

Miller KD et al, NEJM 2007

Eligibility:
- No prior chemo for mets
-Adjuvant taxane if >12 mos.
-HER-2+ only if prior trastuzumab

RANDOMIZE

→ Paclitaxel + bevacizumab

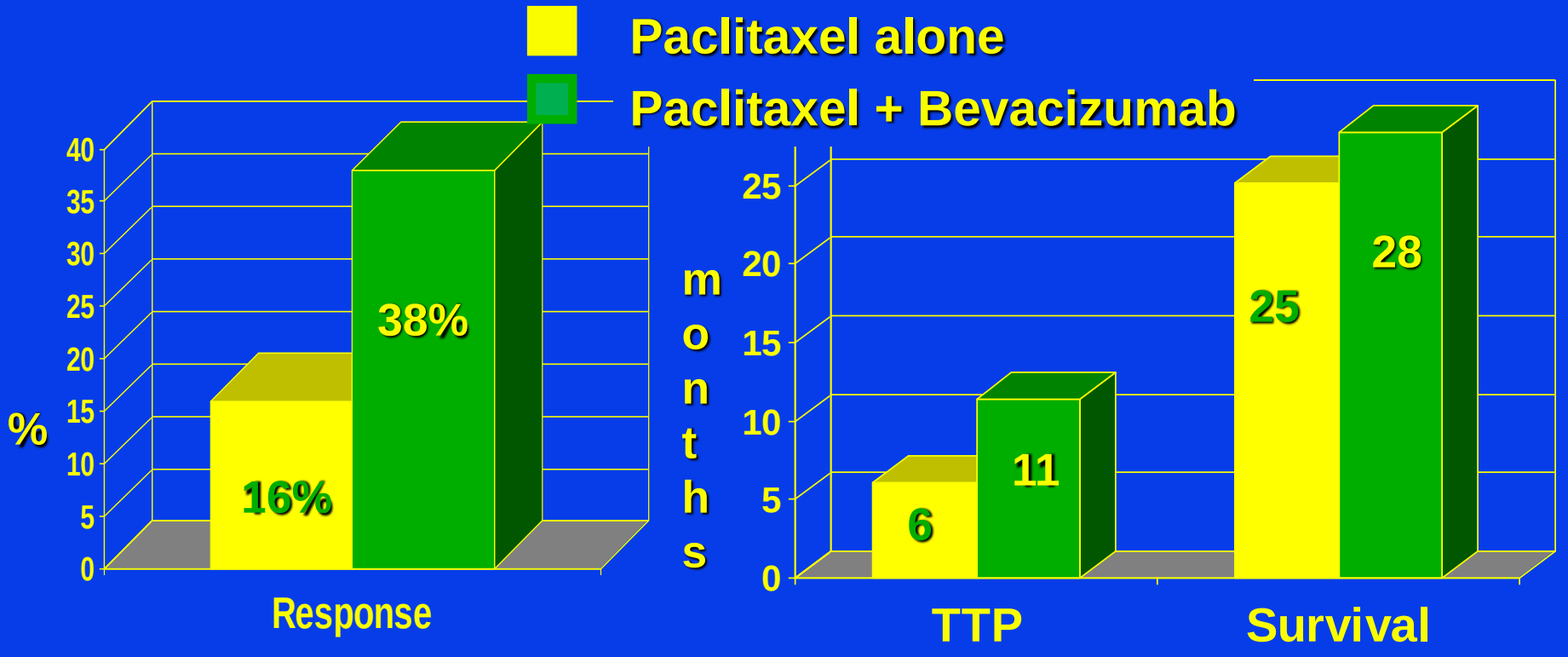
→ Paclitaxel

Accrual: 685

28-day cycle:
Paclitaxel 90 mg/m^2 d1, 8, and 15
Bevacizumab 10 mg/kg d1 and 15

Paclitaxel +/- Bevacizumab in Metastatic Breast Cancer

Miller KD et al, NEJM 357:2666-76, 2007



E2100: Paclitaxel +/- Bevacizumab in Stage IV Breast Cancer

Miller KD et al, NEJM 2007

- Toxicities (grade 3,4)

	Paclitaxel	Paclitaxel + Bev	
HTN	2%	15%	p<0.001
Thrombosis	4%	2%	
Bleeding	0%	2%	p=0.02
Proteinuria	0%	2%	p=0.002

Accelerated FDA approval in 2008

FDA Revoked Approval of Bevacizumab in Breast Cancer

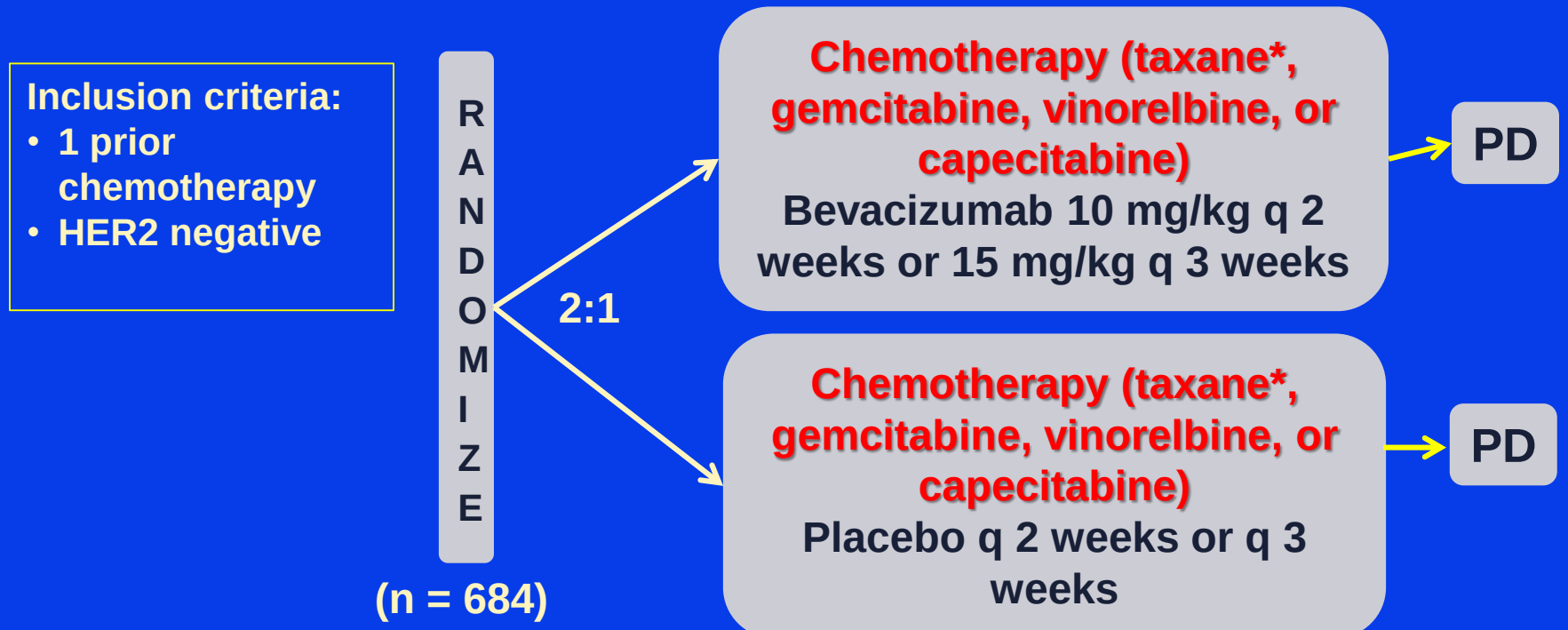
- FDA removed metastatic breast cancer from bevacizumab label
  - No survival benefit
  - Toxic

- Biologic reality?
- Rebound effect?
- Lack of targeting to appropriate population?
  - Which patients?
  - Which tumors?

2nd-Line Bevacizumab

Phase III RIBBON 2 Trial of Chemo/Bevacizumab in 2nd-line HER2-Negative Metastatic Breast Cancer

Brufsky A et al, J Clin Oncol 2011



* Taxane allowed: q 3weekly docetaxel, paclitaxel, or albumin-bound paclitaxel

RIBBON 2: Efficacy

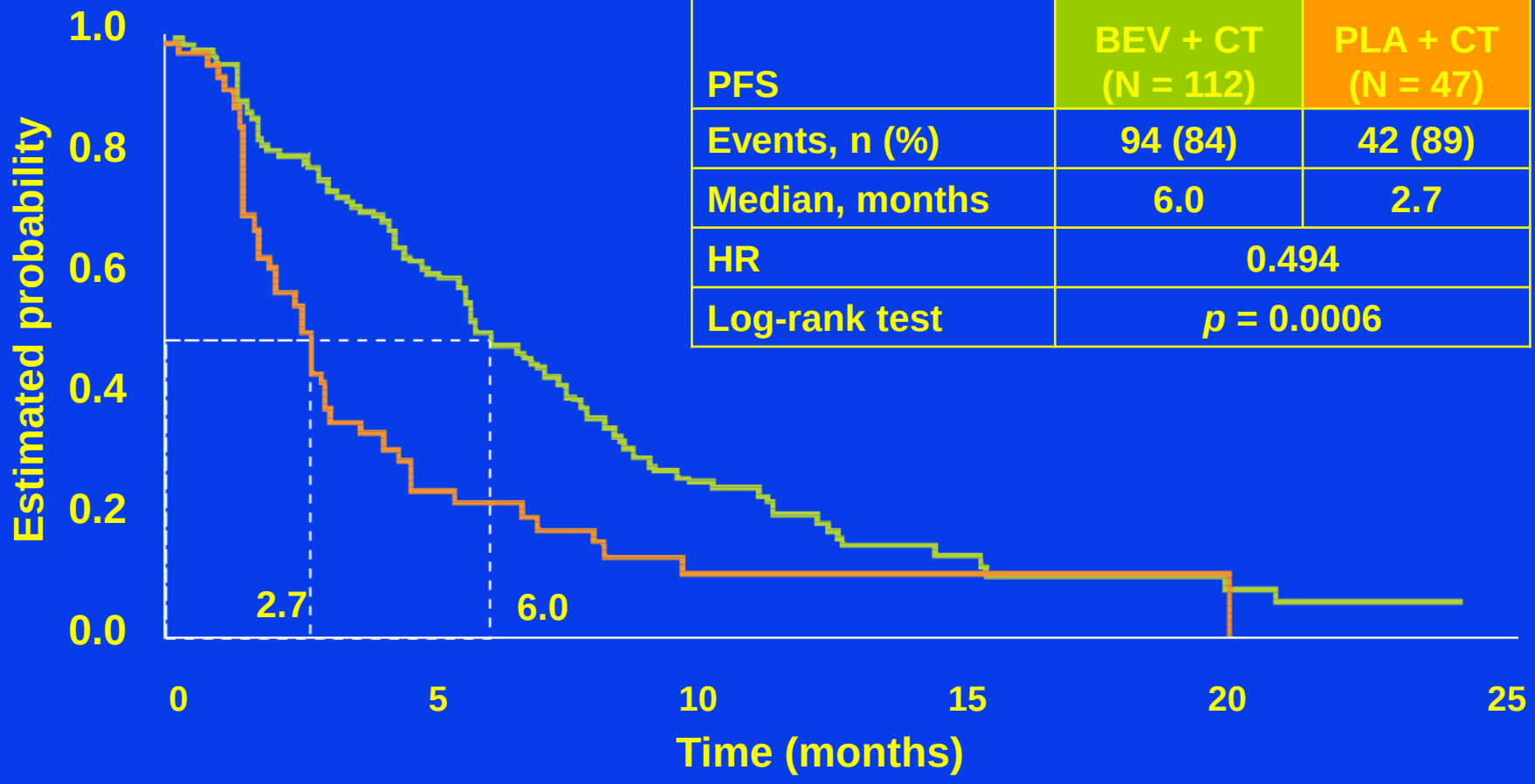
	Chemotherapy/ Placebo	Chemotherapy/ Bevacizumab
Overall Response Rate	30%	39.5%
	P = 0.0193	
Median Progression-Free Survival	5.1 months	7.2 months
	HR 0.78 (95% CI, 0.64-0.93); *P* = 0.0072	
Median Overall Survival (Interim)	16.4 months	18 months
	HR 0.90 (95% CI, 0.71-1.14); *P* = 0.3741	

- Response rate, PFS higher with bevacizumab; OS not statistically different

RIBBON 2: Progression Free Survival in Triple Negative Subgroup

Brufsky A et al, Breast Cancer Res Treatment 2012

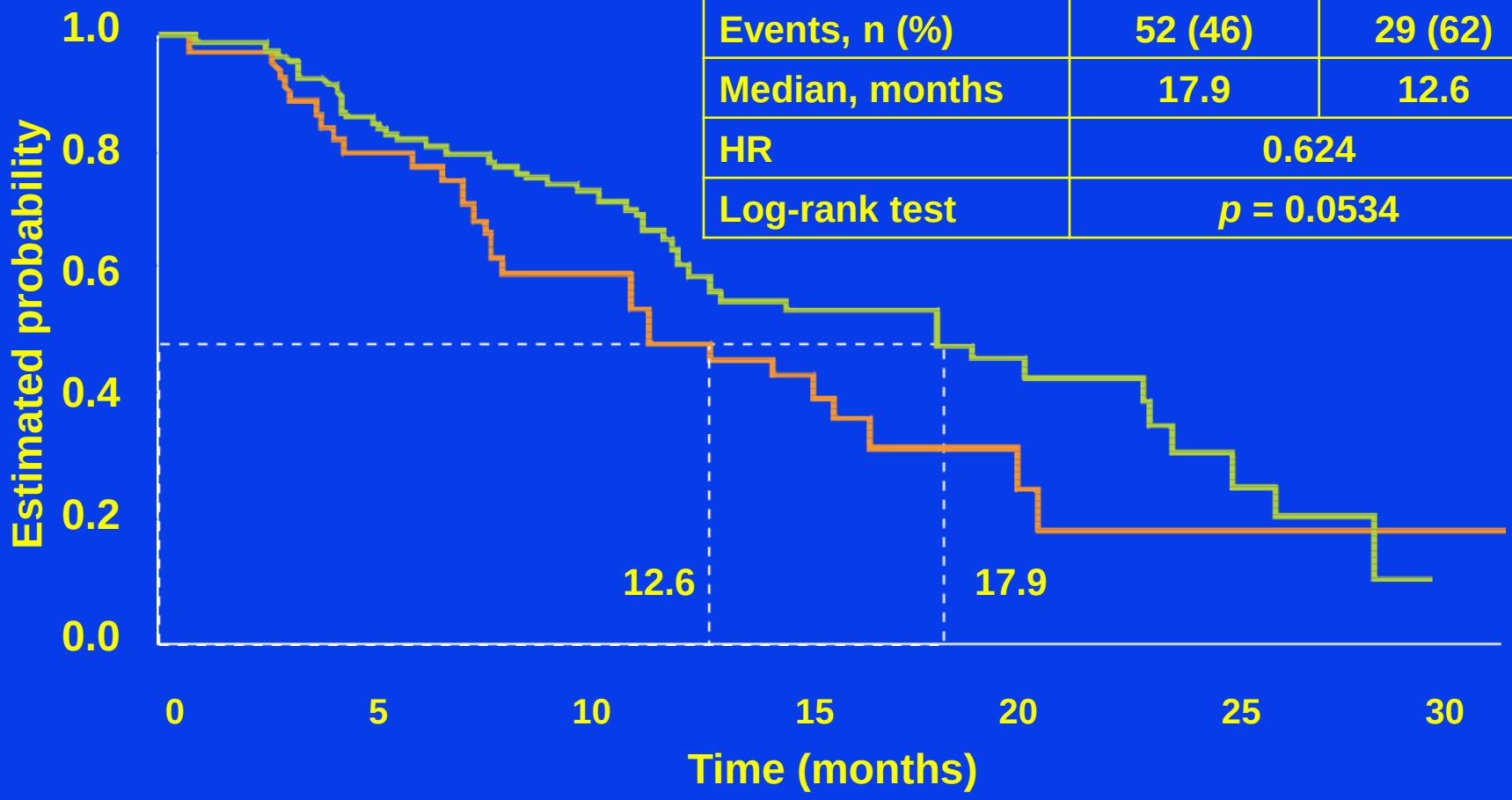
PFS	BEV + CT (N = 112)	PLA + CT (N = 47)
Events, n (%)	94 (84)	42 (89)
Median, months	6.0	2.7
HR	0.494	
Log-rank test	*p* = 0.0006	



RIBBON 2: Interim Overall Survival in Triple Negative Subgroup

Brufsky A et al, Breast Cancer Res Treatment 2012

OS	BEV + CT (N = 112)	PLA + CT (N = 47)
Events, n (%)	52 (46)	29 (62)
Median, months	17.9	12.6
HR	0.624	
Log-rank test	*p* = 0.0534	

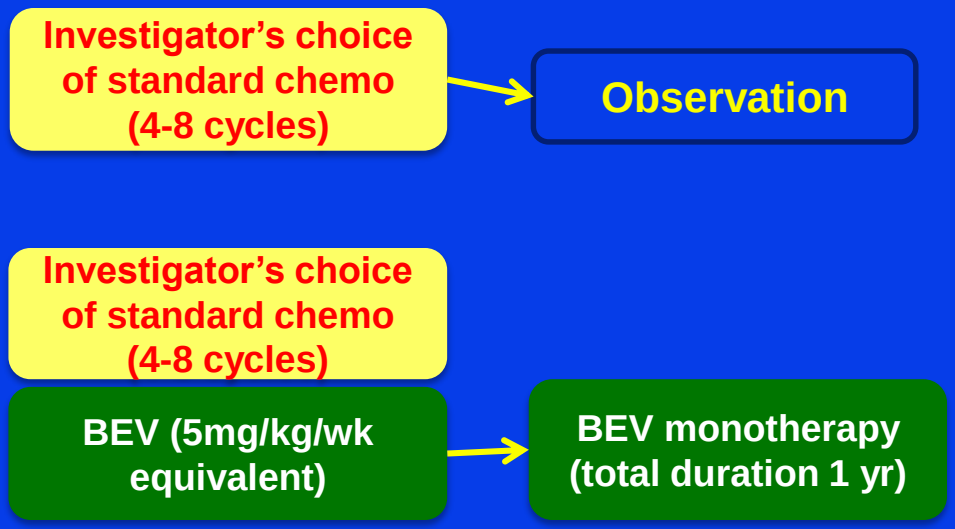


BEATRICE: Phase III Trial of Adjuvant Bevacizumab in Triple Negative Breast Cancer

Cameron D et al, SABCS 2012, Abstract # S6-5

- **Eligibility**
  - Resected invasive breast cancer
  - Negative for ER, PR, HER2 (centrally confirmed)
- **N=2,591**
  - 63% lymph node negative

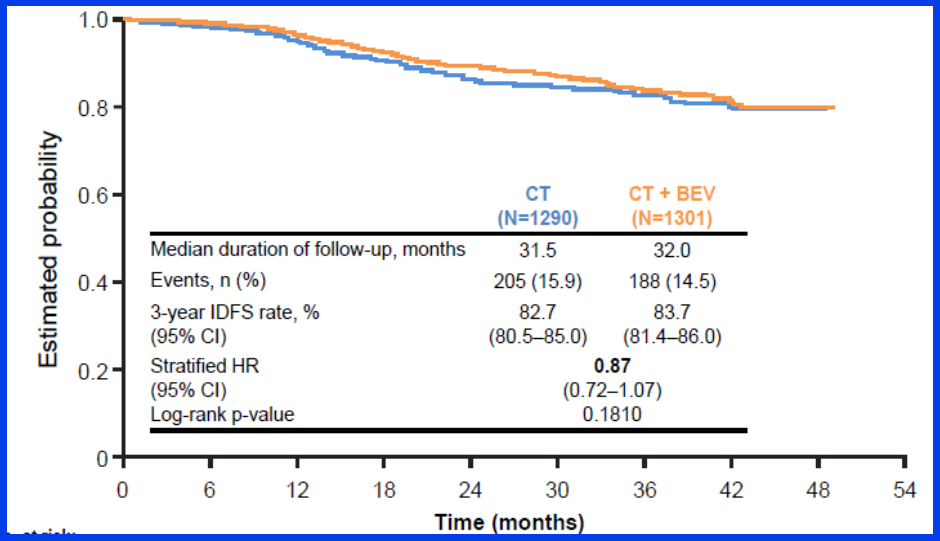
Primary endpoint: invasive disease-free survival



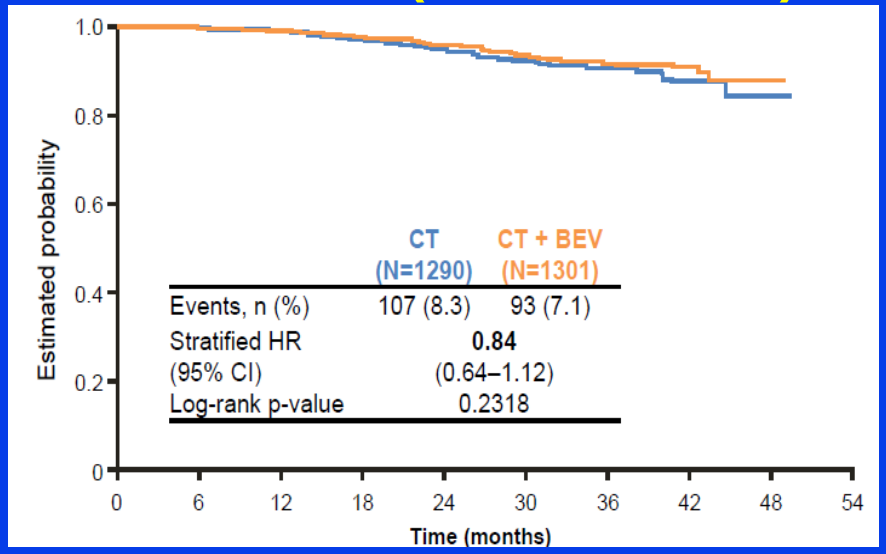
- **Chemotherapy options**
  - Taxane based ≥ 4 cycles
  - Anthracyclline based ≥4 cycles
  - Anthracycline + Taxane (3-4 cycles each)

BEATRICE: Phase III Trial of Adjuvant Bevacizumab in Triple Negative Breast Cancer

Primary Endpoint: IDFS



Interim OS (59% of events)



No improvement in DFS or OS for addition of bevacizumab

BEATRICE: Phase III Trial of Adjuvant Bevacizumab in Triple Negative Breast Cancer

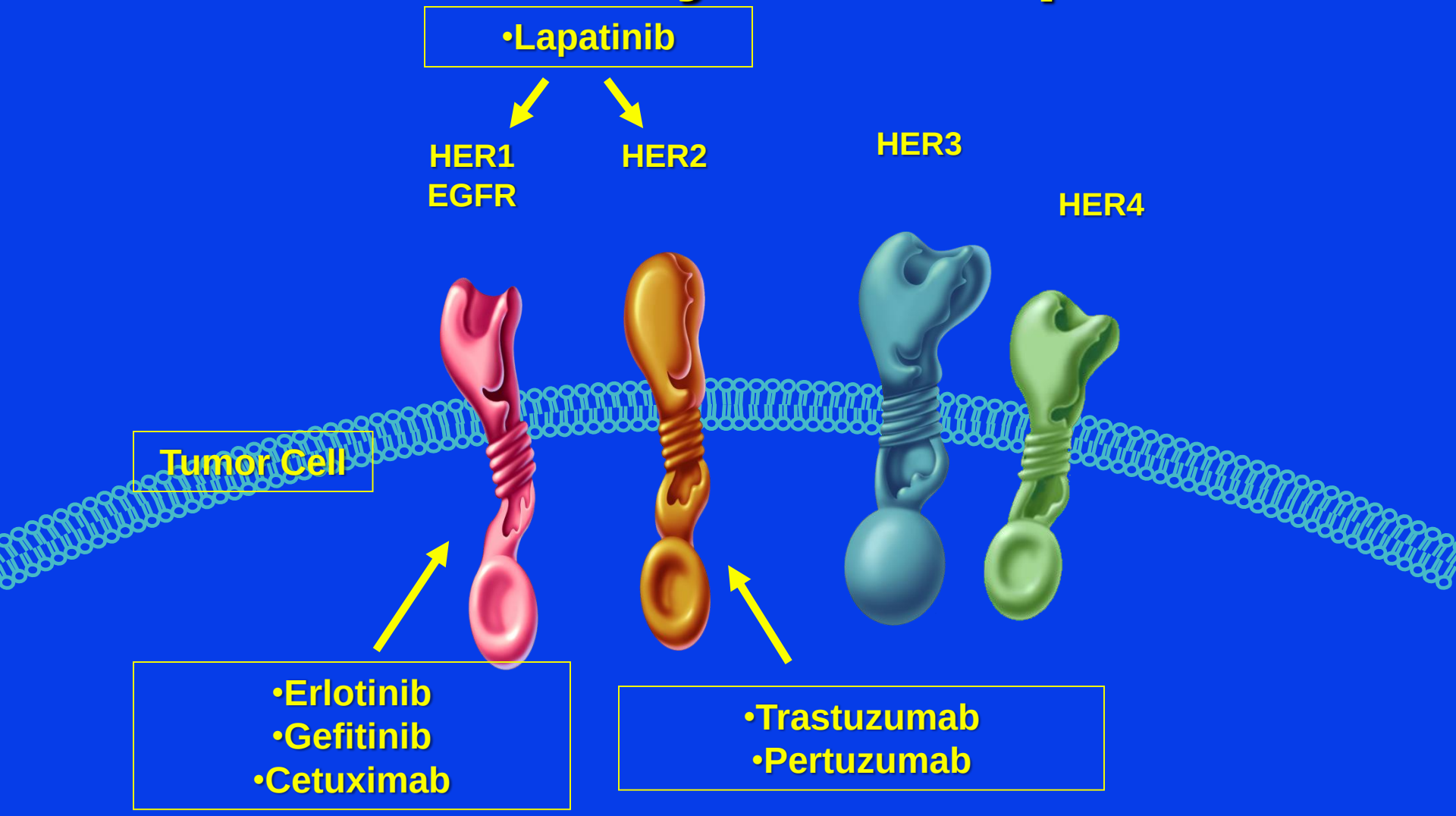
- Disappointing
- 1st randomized Phase III adjuvant trial specifically for triple negative population
- 3 year survival better than anticipated
- No significant improvement in DFS/OS with addition of bevacizumab
- Adverse event profile consistent with that previously seen

Recently Reported Preoperative Trials of Bevacizumab in Breast Cancer

- **NSABP B-40 (Bear H et al) NEJM 2012**
  - **Preop anthracycline/taxane chemotherapy +/- bevacizumab**
  - **Improved pathologic Complete Response (pCR) with bevacizumab: 28.4% vs 34.5%, p = 0.027**
- **Geparquinto (Von Mickwitz G et al) NEJM 2012**
  - **Preop anthracycline/taxane chemotherapy +/- bevacizumab**
  - **Overall (HER2-): pCR 15% vs 17.5% p = ns**
  - **Triple negative subset: pCR 27.8% (no bev) vs 36.4% (with bev) p = 0.21**

Will this translate into improved DFS and OS in the adjuvant trials? Possible reason for optimism?

The Human Epidermal Growth Factor Family of Receptors



EGFR Targeted Therapy in Unselected Metastatic Breast Cancer

	n	RR	CB	TTP
Gefitinib				
Robertson (2003)	33	7%	30%	?
Baselga (2003)	32	0%	6%	8 wks
Albain (2002)	63	2%	5%	8 wks
Erlotinib				
Winer (2002)	69	3%	6%	6 wks

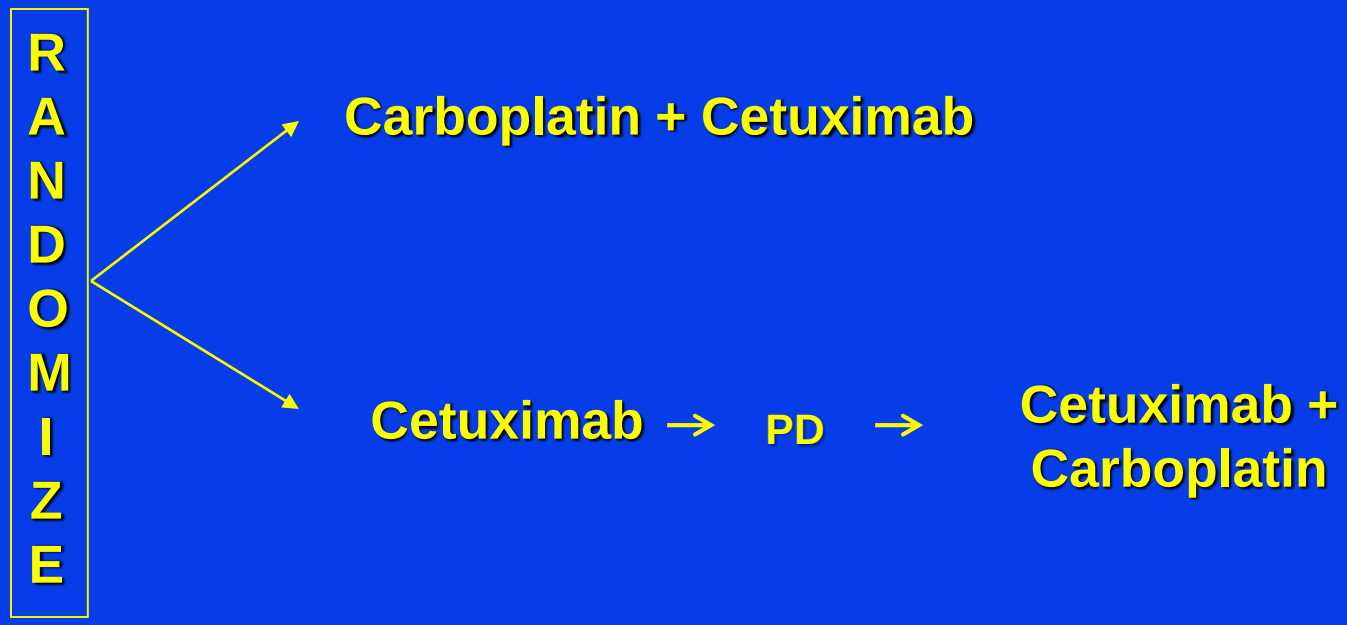
- Conclusions:
  - Minimal clinical activity in heavily pretreated, unselected breast cancer patients
  - Pharmacodynamic results were seen: EGFR signaling pathway is affected in tumor and skin
  - Possible role in “triple negative” population?

TBCRC 001: Randomized Phase II Study of Cetuximab in Combination with Carboplatin in Stage IV TNBC

Carey LA et al, J Clin Oncol 30, 2012

Eligibility:
-Metastatic TNBC

102 patients



TBCRC 001: Randomized Phase II Study of Cetuximab in Combination with Carboplatin in Stage IV TNBC

Carey LA et al, J Clin Oncol 30, 2012

	Cetuxumab	Cetux → Cetux + Carbo	Cetux + Carbo
Complete Response	0	0	1.4%
Partial Response	6%	17%	15%
Stable Disease	16%	25%	23%
Progressive Disease	77%	50%	52%
Overall Response	6%	17%	17%
Clinical Benefit Rate	10%	25%	31%

TBCRC 001: Randomized Phase II Study of Cetuximab in Combination with Carboplatin in Stage IV TNBC

Carey LA et al, J Clin Oncol 30, 2012

- Despite strong preclinical data, combination cetuximab plus carboplatin in metastatic TNBC produced responses in fewer than 20% of patients
- EGFR pathway analysis showed that most TNBCs involved activation
- However, cetuximab blocked expression of the EGFR pathway in only a minority, suggesting that most had alternate mechanisms for pathway activation

Ongoing Study at UW: Combined Targeted Therapies for TNBC: Phase II Trial of Weekly Nab-Paclitaxel and Bevacizumab Followed by Maintenance Bevacizumab and Erlotinib

PI: J Specht

Locally recurrent or metastatic ER/PR/HER2 negative breast cancer; >6 mos from weekly paclitaxel (n=63)

↓

Nab-paclitaxel 100 mg/m^2 IV Qwk x 24 +
Bevacizumab 10 mg/kg IV Q2wk x 8

↓ **CR, PR, SD**

Bevacizumab 10 mg/kg IV Q2wk + Erlotinib 150 mg PO daily

Primary objective: PFS
Secondary objectives: RR, OS, Safety, EGFR, SPARC expression in primary tumor, CTC, CEC

PARP as a Target for Therapy

- **PARP**
  - Enzyme with role in DNA repair
  - Increased levels in triple negative breast cancer
    - » Allows cancer cells to be more resistant to chemotherapy and radiation therapy effects
  - Needed for survival of BRCA-deficient cells

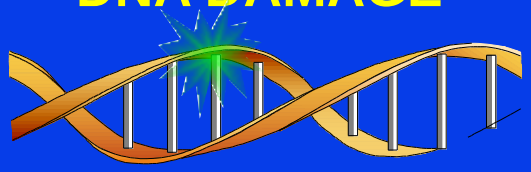
PARP is an Important Enzyme in DNA Repair of Normal Cells as Well as Cancer Cells

Environmental factors
(UV, radiation, chemicals)

Normal physiology
(DNA replication)

Chemotherapy, Radiotherapy

DNA DAMAGE



Cell Death

DNA REPAIR PATHWAYS

Single Strand Breaks
- Base excision repair
- PARP1

Double Strand Breaks
- Homologous recombination
- BRCA1/BRCA2

Replication Lesions
- Base excision repair
- PARP1

DNA Adducts/Base Damage
- Base excision repair
- PARP1

PARP Inhibitors as Therapy in Breast Cancer

- **PARP inhibitors**
  - Potentiate effects of chemotherapy-induced DNA damage
  - Single agent activity in BRCA1/2 deficient tumors
  - Currently being evaluated in clinical trials
- PARP inhibitors with reported clinical data to date:
  - **Iniparib** (BSI-201)
  - **Veliparib** (ABT-888)
  - **Olaparib** (AZD 2281)

Oral PARP Inhibitor Olaparib in BRCA-deficient Advanced Breast Cancer

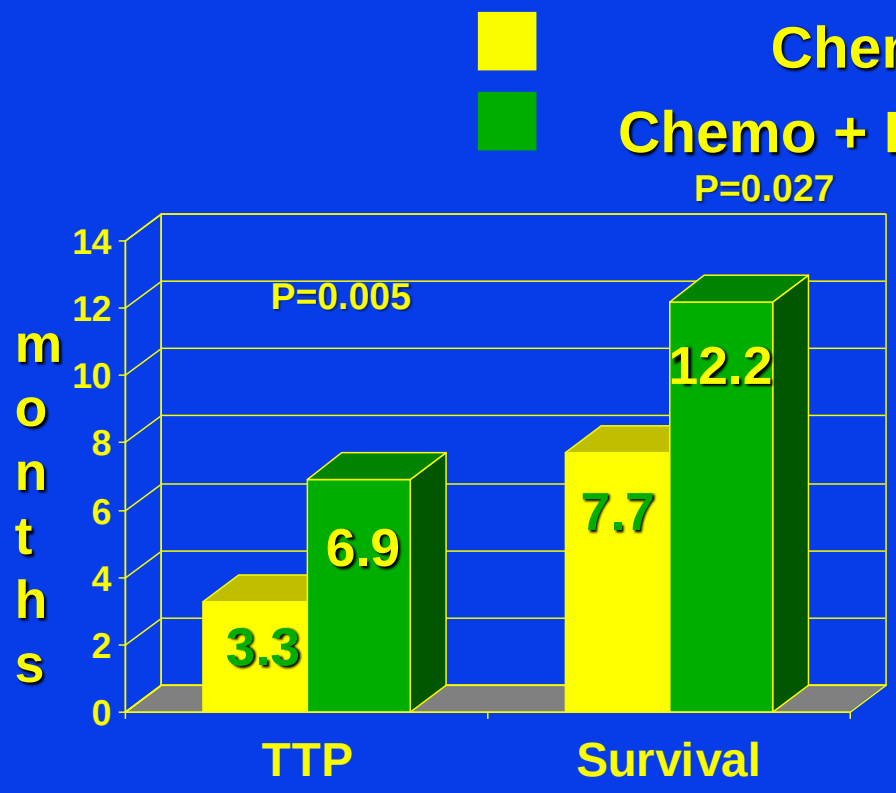
Tutt A et al, ASCO 2009, abstract # 501

- Patients: *BRCA1/ BRCA2* + advanced, chemotherapy refractory breast cancer
- Treatment:
  - Cohort 1: olaparib 400 mg po BID (27 patients)
  - Cohort 2: olaparib 100 mg po BID (27 patients)
- Results:
  - Objective response rate 41%
  - Median PFS: 5.7 months
  - Rare grade 3 nausea, fatigue, vomiting

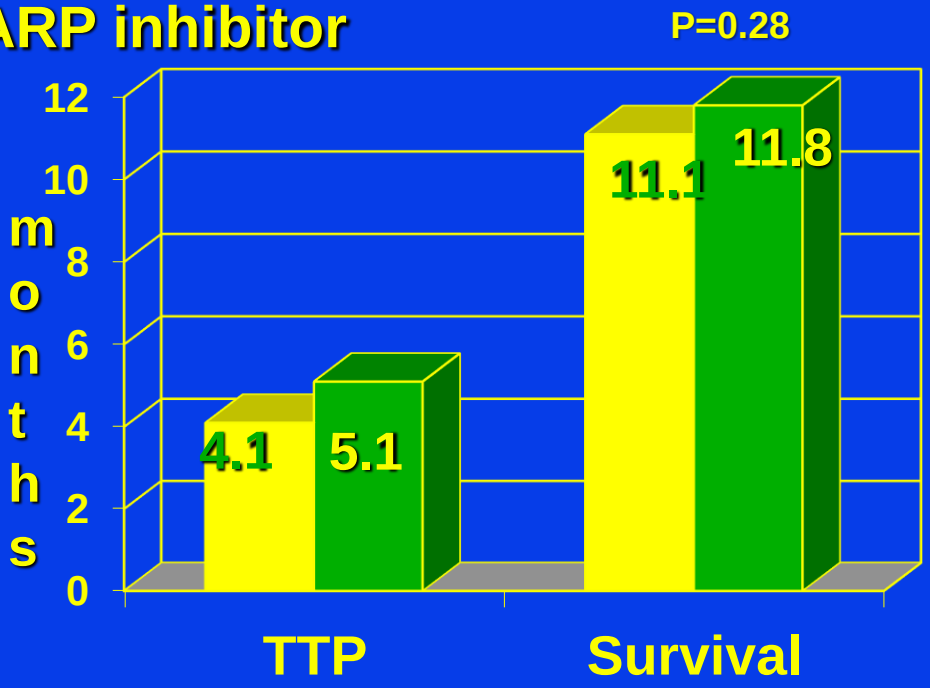
Randomized Phase II vs Phase III Trial Results

Gemcitabine/Carboplatin +/- Iniparib in Triple Negative Metastatic Breast Cancer

O'Shaughnessy et al, NEJM 2011 and ASCO 2011, abstract 1007



Randomized Phase II study



Randomized Phase III study

Far less impressive

Iniparib originally thought to be PARP inhibitor, now uncertain

UW/SCCA Phase I Trial of Cisplatin/Vinorelbine with PARP Inhibitor ABT-888 (Veliparib) in Metastatic Breast Cancer

Rodler E et al, SABCS 2011, abstract P1-17-04

Patients with metastatic TNBC and/or BRCA mutation associated breast cancer

Cisplatin 75 mg/m2 IV Day 1

Vinorelbine 25 mg/m2 Days 1,8

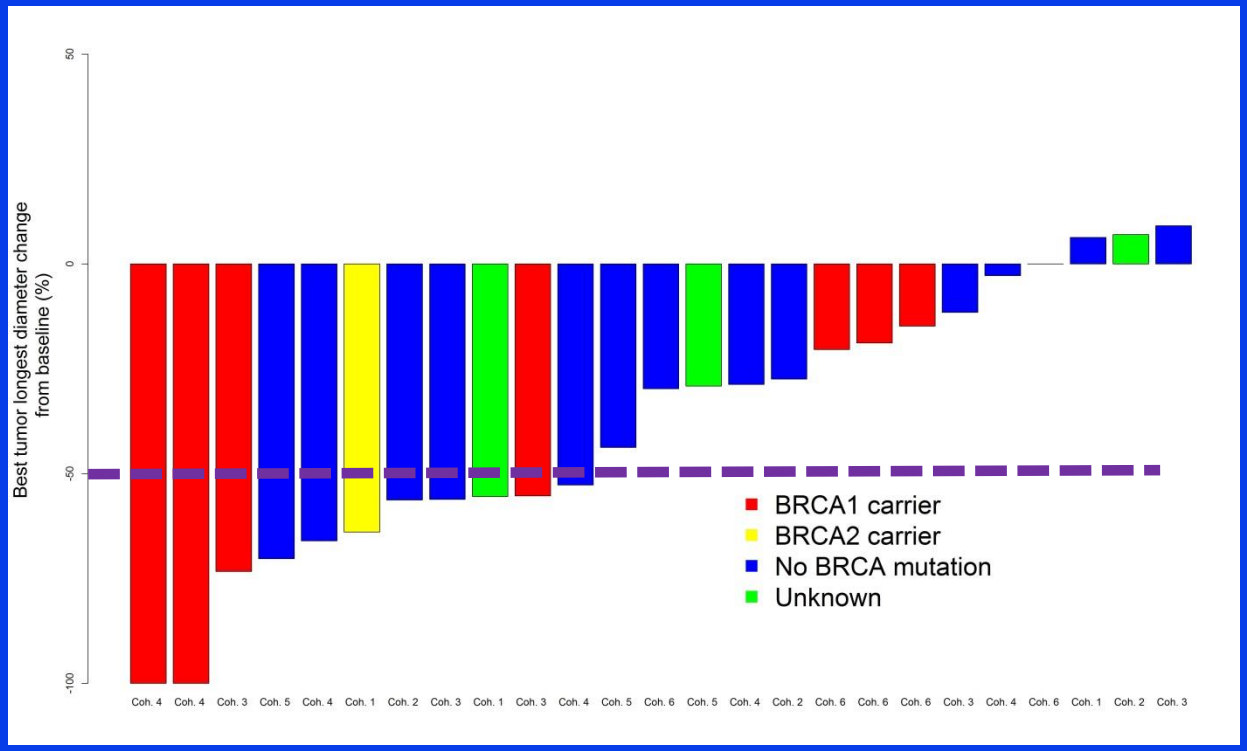
Veliparib Days 1-14 Dose escalation

every 21 days

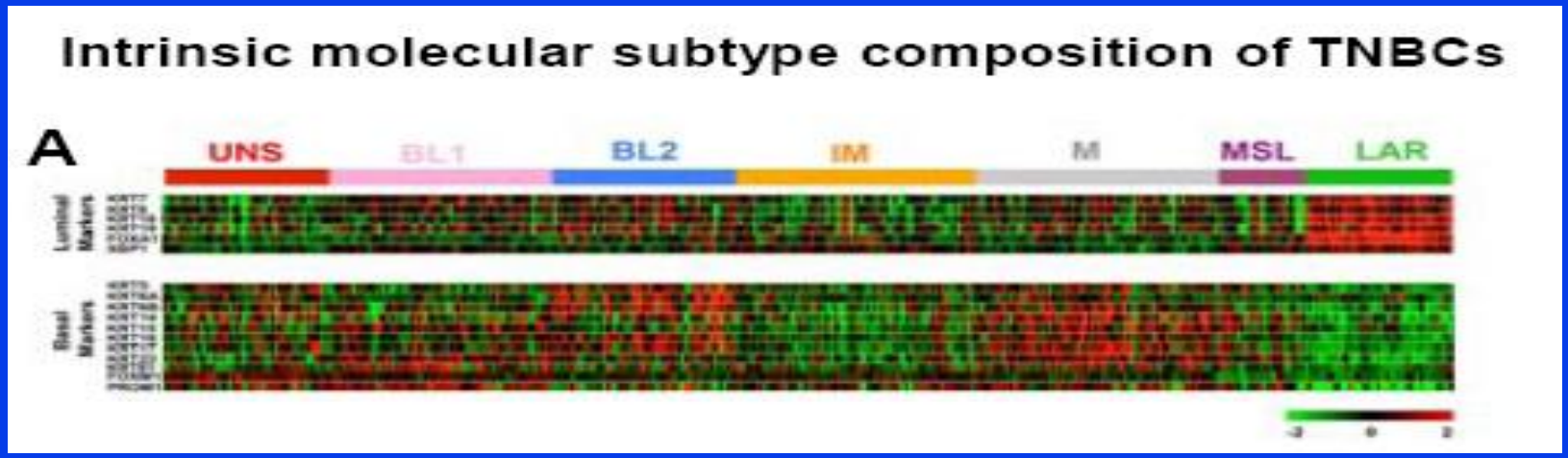
UW/SCCA Phase I Trial of Cisplatin/Vinorelbine with ABT-888 (Veliparib)

Maximum Tumor Response (%) from Baseline

- 36 patients enrolled to date
- Currently at dose level 7 of veliparib



Triple Negative Breast Cancer is a Highly Diverse Group of Cancers



6 subtypes of TNBC identified by gene expression array!

Lehmann BD, et al. J Clin Invest 121:2750-67, 2011

6 Types of Triple Negative Breast Cancer

- **Basal-like 1 and 2 (BL1, BL2)**
  - High expression of cell cycle and DNA response genes
  - More responsive to platinum chemotherapy
- **Immunomodulatory (IM)**
- **Mesenchymal (M) and Mesenchymal-stem Like (MSL)**
  - Enriched for genes associated with epilthelial-mesenchymal transition
  - Responsive to mTOR, PI3K, abl-src pathway drugs
- **Luminal Androgen Receptor (LAR)**
  - Sensitive to androgen receptor drugs

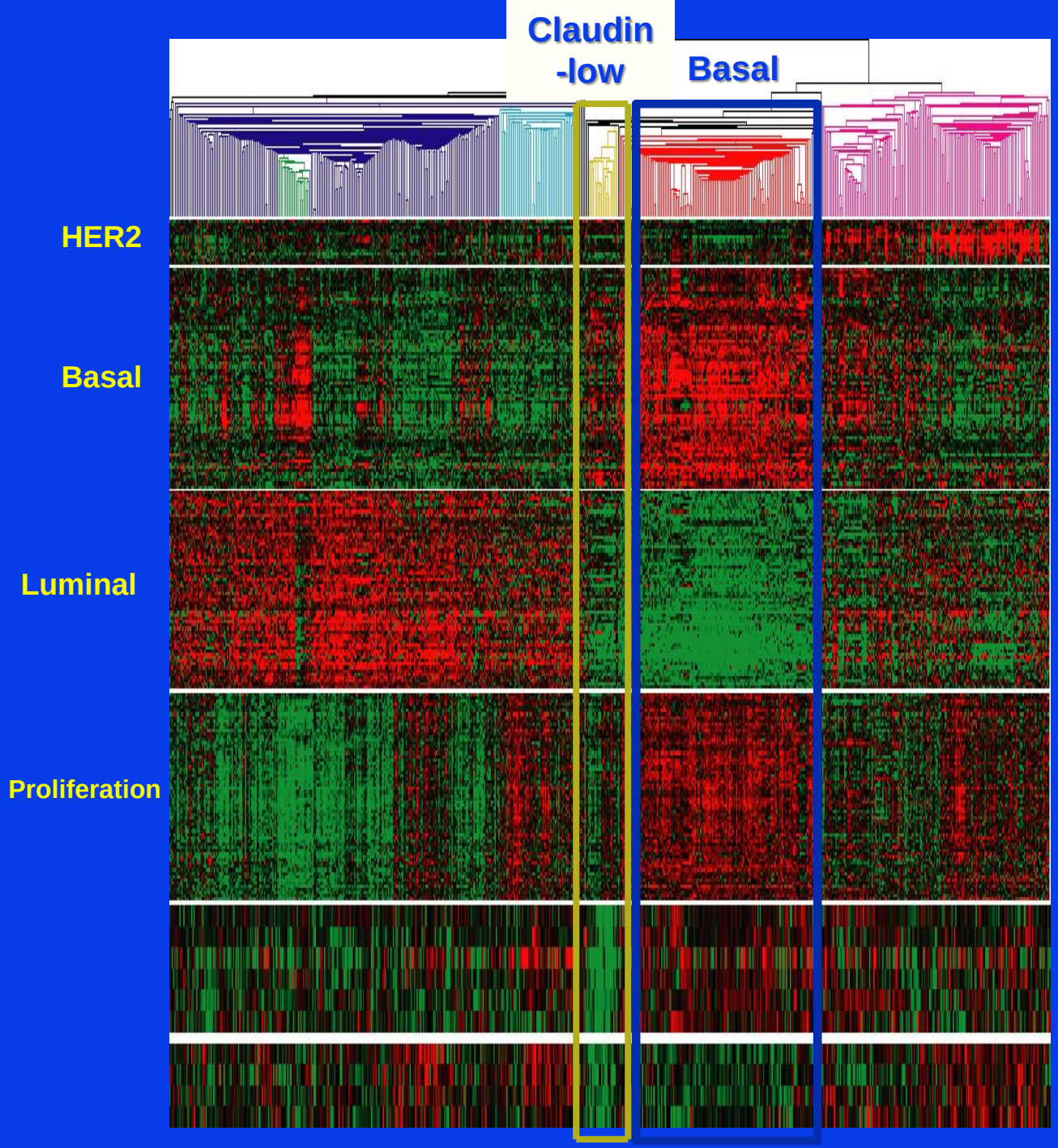
TNBC LAR Subtype

Not Yet Reported TBCRC 011: Targeting Androgen Receptor for the Treatment of AR+/ER-/PR- Metastatic Breast Cancer

Gulcap A et al, ASCO 2011, abstract # 122

- **10-20% of TNBC are Androgen Receptor Positive**
- **Drugs targeting AR are typically used in treating prostate cancer**
  - **Bicalutamide (Casodex)**
  - **Enzalutamide (Xtandi)**

- **TBCRC 011: Treatment with bicalutamide**
- **Study: 230 TNBC patients tested, 27 AR+**
  - **No results to date**



Claudin-low Subtype

- 5-10% of tumors
- Typically ER-, PR-, HER2-
- Low expression of cell-cell junction proteins
- Lymphocyte infiltrates
- Stem cell + EMT features

TNBC M/MSL and Claudin-low Subtypes

Metaplastic Breast Cancer

- Subtype of triple negative breast cancer
  - Rare, but increasing incidence
- Distinct subtype by molecular profiling
  - Claudin-low
  - Enriched for epithelial-to-mesenchymal transition (EMT) markers
  - ~50% of tumors have PI3K mutations or loss in PTEN
  - Increased VEGF production
- Chemorefractory
  - ≤10% pCR rate with neoadjuvant chemotherapy
  - Little data regarding response in metastatic setting

DAT in Advanced Cancers Cancer

Moroney J et al, Clin Cancer Res 18, 2012

- 136 patients with advanced cancer
  - 29 breast cancer (12 metaplastic)
- Regimen
  - Liposomal doxorubicin (**D**oxil) 30mg/m^2 IV every 3 weeks
  - Bevacizumab (**A**vastin) 15mg/kg IV every 3 weeks
  - Temsirolimus (**T**orisel) 25mg IV weekly
- Results
  - Response in metaplastic breast cancer: 5/12 (42%)

TNBC M/MSL and Claudin-low Subtypes

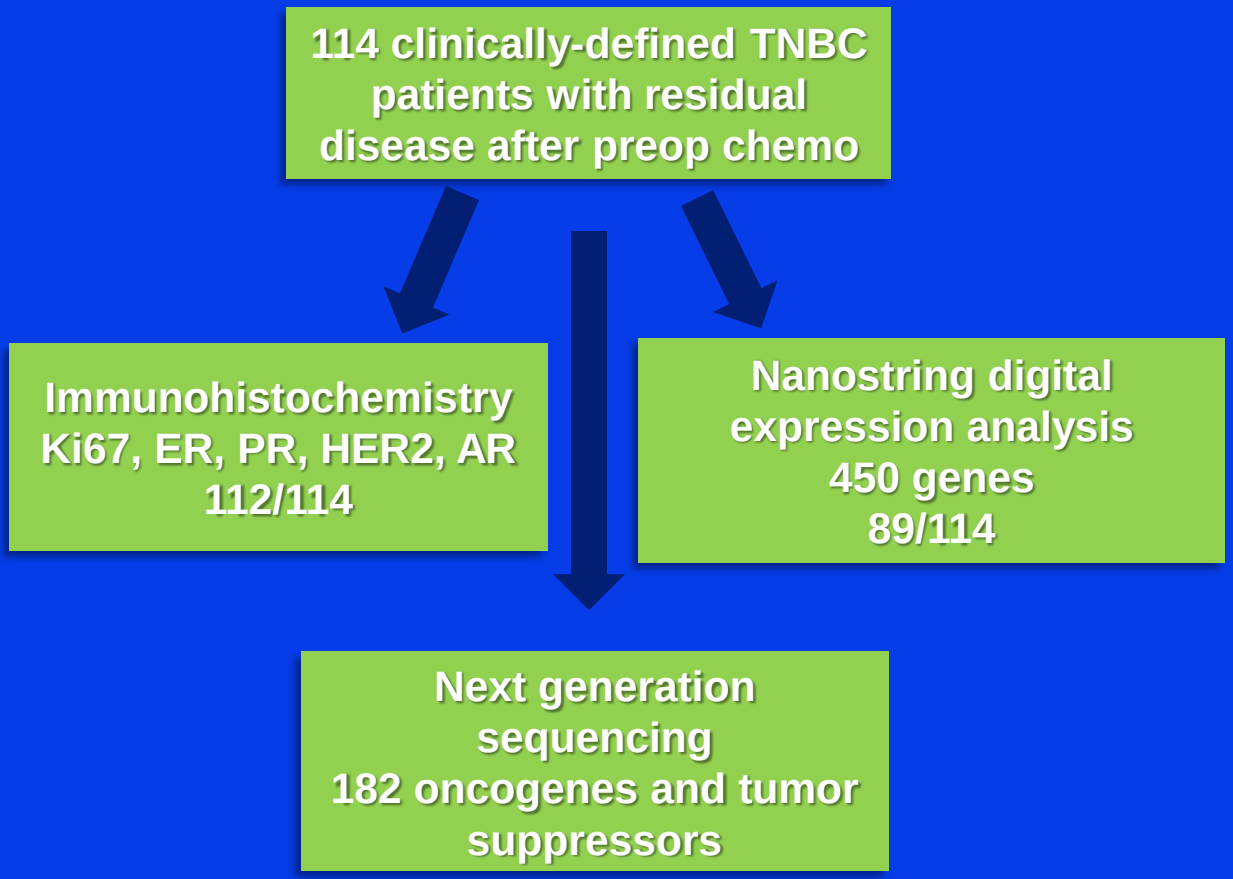
Proposed SWOG Clinical Trial: DAT for Metaplastic Triple Negative Breast Cancer

PI: S Moulder

- Triple negative, metastatic breast cancer
  - High grade metaplastic, spindle cell, or myoepithelial histology
  - Vimentin positive
  - 'Claudin-low' or Mesenchymal-like tumors by profiling
- Regimen: DAT vs liposomal doxorubicin
  - Liposomal doxorubicin (**D**oxil) 30mg/m^2 IV every 3 weeks
  - Bevacizumab (**A**vastin) 15mg/kg IV every 3 weeks
  - Temsirolimus (**T**orisel) 25mg IV weekly

Molecular Characterization of Residual Triple Negative Breast Cancer after Preoperative Chemotherapy

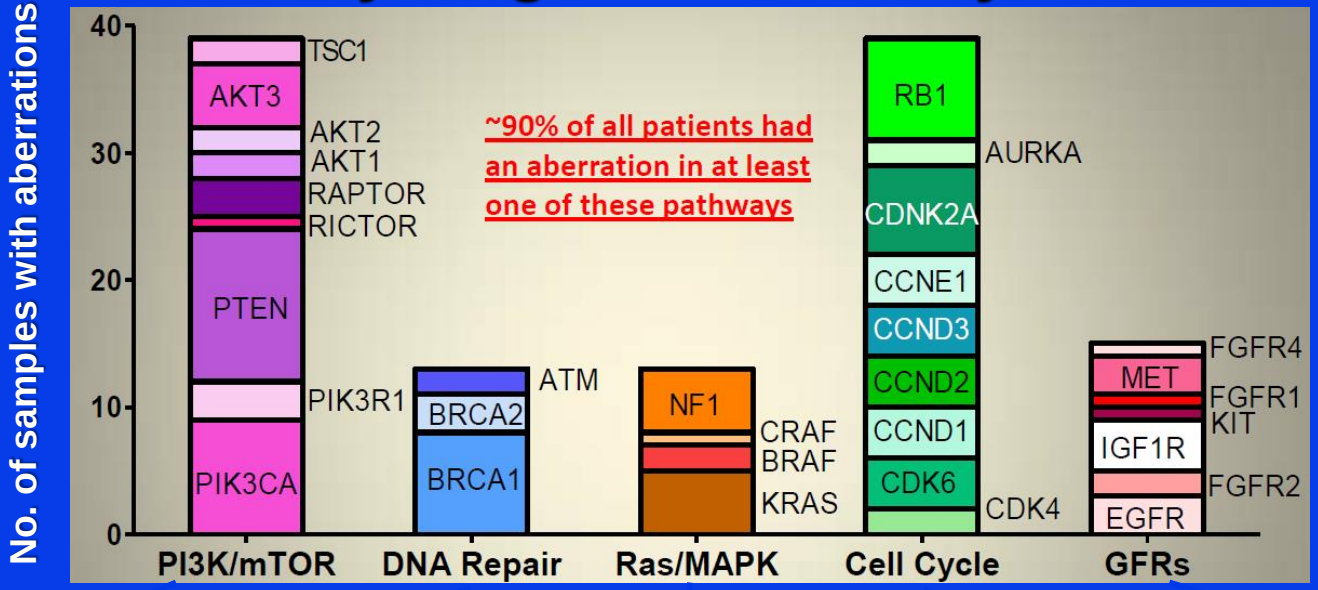
Balko JM et al, SABCS 2012 Abstract # S3-6



Molecular Characterization of Residual Triple Negative Breast Cancer after Preoperative Chemotherapy

Balko JM et al, SABCS 2012 Abstract # S3-6

Clinically Targetable Pathways in TNBC



PI3K/mTOR inhibitors

DNA repair-targeting agents

RAF/MEK inhibitors

Cell cycle/ mitotic spindle inhibitors

Targeted RTK inhibitors

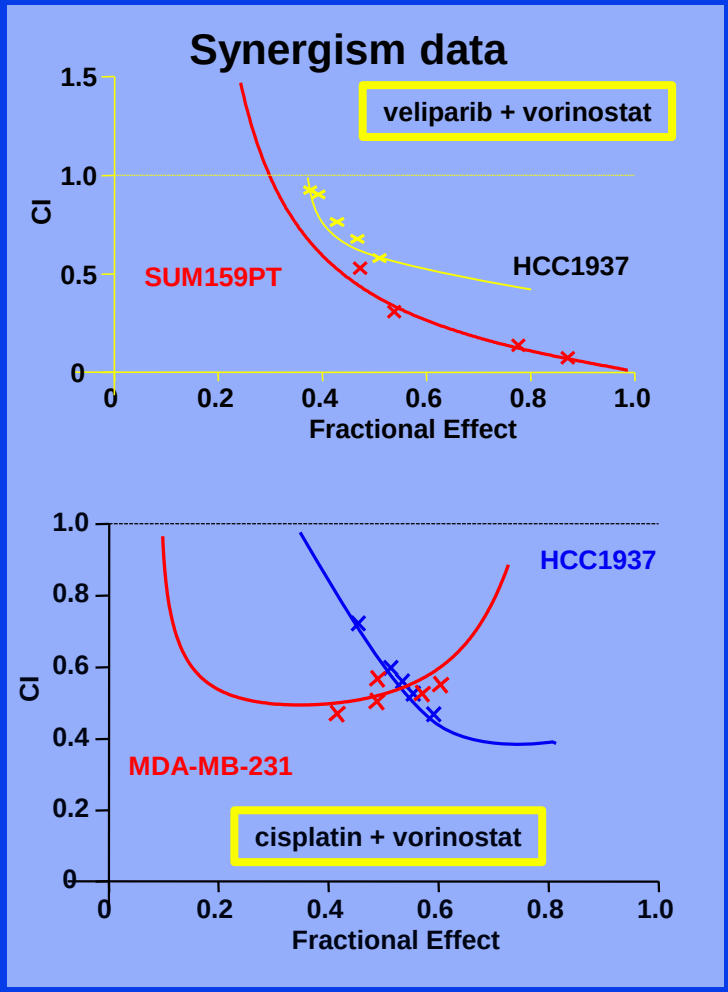
These data show that TNBC after preoperative chemotherapy is heterogeneous and has multiple alterations that are targetable with existing drugs in development

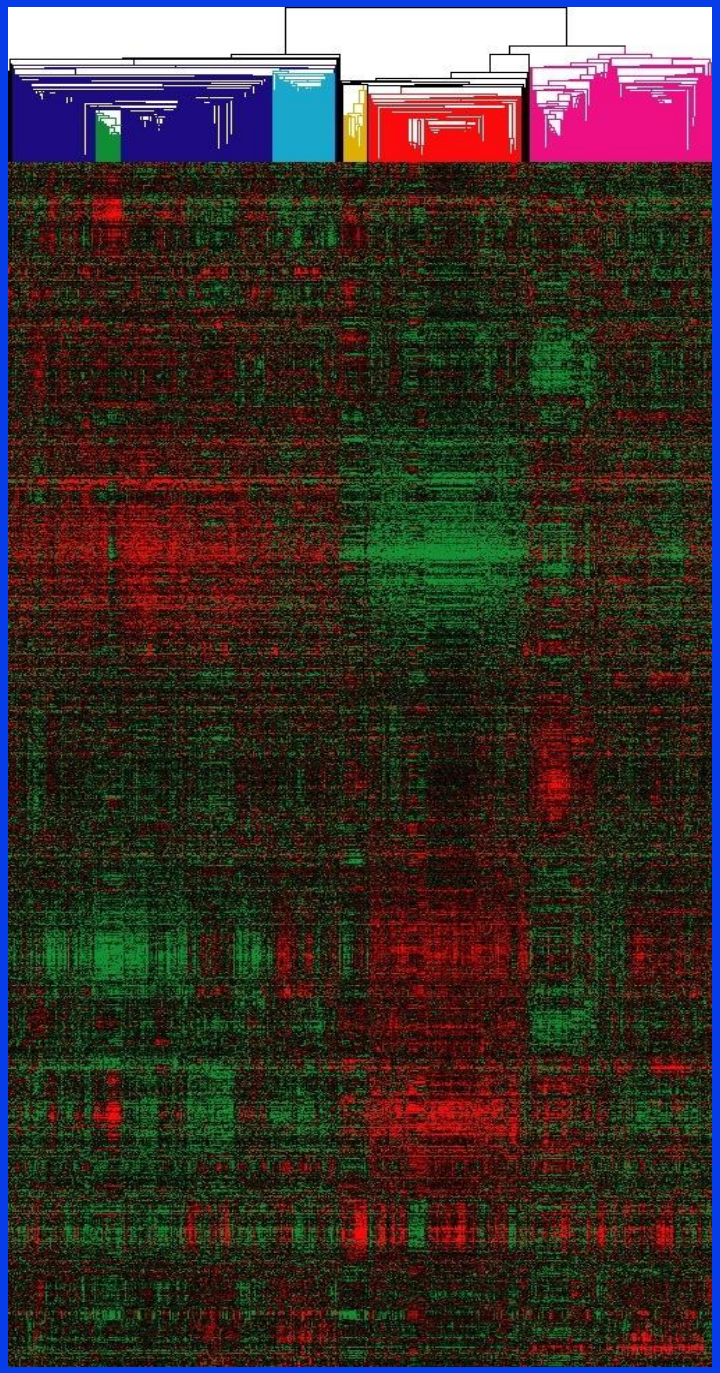
Treatment with Histone Deacetylase Inhibitors Creates 'BRCAness' and Sensitizes Triple Negative Breast Cancer Cells to PARP Inhibitors and Cisplatin

Bhalla KN et al, SABCS 2012 Abstract # S3-7

- **Methods:**
  - Used human triple negative cell lines
    - » BRCA-mutant (SUM159PT)
    - » BRCA non-mutant (MDA-MB-231, HCC1937)
  - Treated with HDACi (vorinostat), PARPi (veliparib), & cisplatin
- **Results:**
  - Vorinostat synergistically enhanced PARPi and cisplatin-induced induced DNA strand breaks and apoptosis
  - Synergistic inhibition in TNBC cells (CIs <1.0)

Supports evaluation of HDAC inhibitors with PARP inhibitors and cisplatin in TNBC





Triple-Negative Tumor Conclusions

1. Triple-negative breast cancers are a heterogeneous group primarily composed of Basal-like breast tumors

2. Claudin-low tumors are also a major constituent of Triple-negative cancers

3. Chemotherapy benefit is typically high, although subsets have little chemo benefit

4. Many biologically targeted agents are being tested on this group including PARP inhibitors, angiogenesis inhibitors, HER1/EGFR and mTOR/PI3K pathway inhibitors

Treatment of Triple Negative Breast Cancer: The Future is Looking Up!