Update on
Triple Negative Breast Cancer

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The Breast Cancer Layer Cake
Important subsets of breast cancers defined by molecular markers and by clinical treatment options

- All Breast Cancer
- ER+
- HER2+
- Basaloid
Basal (Triple-Negative) Breast Cancer

- ER, PR, and HER2-negative (“triple negative”)
- High nuclear grade and proliferative indices
- BRCA-1 Positive
- Ethnic component
- Chemosensitive but poor prognosis
- Differential chemosensitivity?
The growing impact of Triple-Negative/Basal-like Breast Cancers

- TNBC in PubMed
- Basal and Breast in PubMed
- TNBC Clinical Trial in ClinicalTrials.gov (103 open)
- Inherited mutation
- 1/500 to 1/1000 in general population
- 1/50 in Jewish populations
- Mutation affects DNA damage repair
- Responsible for 1-2% of breast cancers
- Lifetime breast cancer risk 50 – 85%
- More aggressive tumors at younger ages
- Increases other cancer risks (ovarian)
Family History: Testing Considerations

- Know BRCA mutations
- Multiple close relatives with breast or ovarian cancer
- Breast cancer before the age of 50
- Both breast and ovarian cancer
- Bilateral breast cancer
- Close relatives with multiple cancers
- Male breast cancer

Saslow et al. CA 2007
Prophylactic Mastectomy

• Decreases breast cancer risk by 95%
• Consider only after significant counseling
• ASSO guidelines:
  – BRCA or other genetic mutations
  – Strong family history
  – ADH, ALH, LCIS on biopsy
  – Difficult surveillance such as excessively dense breasts
Salpingo-oophorectomy

- Considered in known BRCA 1 or 2
- 80-95% reduction in ovarian cancer
- 50% reduction in breast cancer
- Negative effects
  - Menopausal symptoms
  - Increase cardiovascular risk
  - Accelerated bone loss
  - Decreased quality of life measures
Screening Tools

• Mammography
• Breast self-examination
• Clinical breast examination
• Digital mammography
• US
• MRI
Figure 1. Age-specific Female Breast Cancer Incidence (2004-2008) and Mortality (2003-2007) Rates

Sources: Incidence: North American Association of Central Cancer Registries. Mortality: National Center for Health Statistics, Centers for Disease Control and Prevention, as provided by the Surveillance, Epidemiology, and End Results Program, National Cancer Institute.

American Cancer Society, Surveillance Research, 2011
Carolina Breast Cancer Study (CBCS)
Population-based case-control study

- 40% African-American / 60% Caucasian
- 50% under the age of 50 at diagnosis

1424 cases with IHC for ER, PR, HER2, CK5/6, HER1, pathology data, TP53 and BRCA1 mutation data
Distribution of breast cancer subtypes according to race and menopausal status using 1424 cases: invasive (1000) and \textit{in-situ} (424) breast cancers

<table>
<thead>
<tr>
<th>Breast cancer subtype</th>
<th>African-American Premenopausal N (%)</th>
<th>African-American Postmenopausal N (%)</th>
<th>Caucasian Premenopausal N (%)</th>
<th>Caucasian Postmenopausal N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A N = 796</td>
<td>108 (41.4%)</td>
<td>179 (56.3%)</td>
<td>216 (57.4%)</td>
<td>293 (66.5%)</td>
</tr>
<tr>
<td>Basal-like N = 225</td>
<td>70 (27.2%)</td>
<td>52 (16.0%)</td>
<td>54 (14.5 %)</td>
<td>49 (9.3%)</td>
</tr>
<tr>
<td>HER2+/ER- N = 116</td>
<td>22 (8.4%)</td>
<td>26 (7.7%)</td>
<td>24 (5.6%)</td>
<td>44 (6.0%)</td>
</tr>
<tr>
<td>Luminal B N = 137</td>
<td>19 (7.3%)</td>
<td>26 (8.7%)</td>
<td>46 (12.4%)</td>
<td>46 (10.7%)</td>
</tr>
<tr>
<td>Unclassified N = 150</td>
<td>41 (15.7%)</td>
<td>38 (11.3%)</td>
<td>38 (10.1%)</td>
<td>33 (7.5%)</td>
</tr>
<tr>
<td>Total: 1424 P &lt; 0.0001</td>
<td>260 (100%)</td>
<td>321 (100%)</td>
<td>378 (100%)</td>
<td>465 (100%)</td>
</tr>
</tbody>
</table>
### Epidemiology of basal-like breast cancer, Millikan et al., Breast Cancer Research and Treatment, 2008 (PMID 17578664)

**Adjusted ORs (95% CI)**

N = 1424 cases and 2022 controls

<table>
<thead>
<tr>
<th></th>
<th>Luminal A N=796</th>
<th>Basal-like N=225</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menarche &lt; 13</td>
<td>1.1 (0.9-1.3)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
<tr>
<td>≥ 3 children</td>
<td>0.7 (0.5-0.9)</td>
<td>1.9 (1.1-3.3)</td>
</tr>
<tr>
<td>First birth &lt; 26</td>
<td>0.7 (0.5-0.9)</td>
<td>1.9 (1.2-3.2)</td>
</tr>
<tr>
<td>Breastfeeding ≥ 4m</td>
<td>0.9 (0.7-1.1)</td>
<td>0.7 (0.4-0.9)</td>
</tr>
<tr>
<td>Parity ≥ 3 and No breastfeeding</td>
<td>0.7 (0.5-0.9)</td>
<td>1.9 (1.1-3.3)</td>
</tr>
<tr>
<td>Waist:Hip ≥ 0.84</td>
<td>1.5 (1.1-1.9)</td>
<td>2.3 (1.4-3.6)</td>
</tr>
</tbody>
</table>
Triple-Negative Breast Cancer

Standard of Care: CT → CT → CT

Major Questions:
1. Which chemotherapy?
2. How long?
3. Combination or sequential?
## New Drugs for Breast Cancer

### 1980s:
- Mitoxantrone

### 1990s:
- AIs (metastatic)
- Goserelin
- Zoledronate
- Taxanes (metastatic)
- Epirubicin (adjuvant)
- Vinorelbine
- Gemcitabine
- Liposomal doxorubicin
- Capecitabine
- Dexrazoxane (cardiac toxicity)

### 2000s:
- AIs (adjuvant)
- Fulvestrant
- Docetaxel (adjuvant)
- Paclitaxel (adjuvant)
- N-ab paclitaxel
- Ixabepilone
- Trastuzumab (adjuvant)
- Lapatinib
- Bevacizumab
- Eribulin
- Denosumab

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**Mostly chemotherapy**
- Mostly stage IV

**Adjuvant (early) treatment**
- Chemotherapy, endocrine, targeted Rx

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## Variable Response to Chemotherapy Regimen

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Regimen</th>
<th>T-FAC$^1$ (N=82)</th>
<th>AC-T$^2$ (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A/B</td>
<td></td>
<td>2/30 (7%)</td>
<td>4/62 (7%)</td>
</tr>
<tr>
<td>Normal-like</td>
<td></td>
<td>0/10 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>HER2+/ER-</td>
<td></td>
<td>9/20 (45%)</td>
<td>4/11 (36%)</td>
</tr>
<tr>
<td>Basal-like</td>
<td></td>
<td>10/22 (45%)</td>
<td>9/34 (26%)</td>
</tr>
</tbody>
</table>

1 Rouzier et al, Clin Cancer Res 2005; 2 Carey LA et al, SABCS 2004

$P<0.001$  $P=0.003$
BRCA1 Tumors Are More Sensitive to Anthracyclines Than Sporadic Triple Negatives

<table>
<thead>
<tr>
<th></th>
<th>BRCA1 Mutated FEC Regimen (n = 19)</th>
<th>Controls FEC Regimen (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>37 (25-48)</td>
<td>49 (29-66)</td>
</tr>
<tr>
<td>Median T, mm</td>
<td>55 (32-90)</td>
<td>50 (30-120)</td>
</tr>
<tr>
<td>ER negative, %</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>Grade 3, %</td>
<td>83</td>
<td>86</td>
</tr>
<tr>
<td>Median NBR cycles</td>
<td>4 (3-6)</td>
<td>4 (3-6)</td>
</tr>
<tr>
<td>PCR rate, %*</td>
<td>47</td>
<td>22</td>
</tr>
<tr>
<td>pN+, %</td>
<td>16</td>
<td>40</td>
</tr>
</tbody>
</table>

*P = .03

## Chemotherapy Duration Matters: Progression-Free Survival

### Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Longer Better</th>
<th>Shorter Better</th>
<th>% Weight</th>
<th>HR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coates 1987</td>
<td></td>
<td></td>
<td>13</td>
<td>0.56</td>
<td>0.44-0.71</td>
</tr>
<tr>
<td>Harris 1990</td>
<td></td>
<td></td>
<td>2</td>
<td>1.18</td>
<td>0.65-2.15</td>
</tr>
<tr>
<td>Muss 1991</td>
<td></td>
<td></td>
<td>3</td>
<td>0.26</td>
<td>0.16-0.43</td>
</tr>
<tr>
<td>Ejlertsen 1993</td>
<td></td>
<td></td>
<td>28</td>
<td>0.71</td>
<td>0.61-0.83</td>
</tr>
<tr>
<td>Gregory 1997</td>
<td></td>
<td></td>
<td>10</td>
<td>0.70</td>
<td>0.53-0.92</td>
</tr>
<tr>
<td>Falkson 1998</td>
<td></td>
<td></td>
<td>5</td>
<td>0.46</td>
<td>0.31-0.68</td>
</tr>
<tr>
<td>Bastit 2000</td>
<td></td>
<td></td>
<td>11</td>
<td>0.65</td>
<td>0.50-0.84</td>
</tr>
<tr>
<td>Nooij 2003</td>
<td></td>
<td></td>
<td>8</td>
<td>0.67</td>
<td>0.50-0.90</td>
</tr>
<tr>
<td>Gennari 2006</td>
<td></td>
<td></td>
<td>6</td>
<td>1.01</td>
<td>0.71-1.43</td>
</tr>
<tr>
<td>Majordomo 2009</td>
<td></td>
<td></td>
<td>8</td>
<td>0.77</td>
<td>0.57-1.05</td>
</tr>
<tr>
<td>Alba 2010</td>
<td></td>
<td></td>
<td>6</td>
<td>0.53</td>
<td>0.37-0.76</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>100</td>
<td>0.64</td>
<td>0.55-0.76</td>
</tr>
</tbody>
</table>

Test for heterogeneity, $P = .001$  
Test for treatment effect, $P < .001$

Sequential or Combination Therapy for Advanced Breast Cancer?
ECOG 1193: First-line Chemotherapy for Advanced Breast Cancer: Monotherapy vs Combination Therapy

Response rates: A = 36%, T = 34%, AT = 47%

Advantages of Combination (Chemo)Therapy

• Higher response rate/longer TTP for initial choice of regimen
• Better for visceral crisis?

Advantages of Monotherapy

• You know what is working (or not)
• There is less toxicity
• You know what is causing toxicity
• You can adjust dose in a rational fashion
• Costs are less
• No apparent compromise on survival
Insulin and Breast Cancer Prognosis

Death $p=0.001$
Distant Recurrence $p=0.007$

Insulin Quartiles (pmol/L)

Molecular Action of Insulin

Adapted from Vigneri P et al., Endocr Relat Cancer 2009 Jul 20 (epub ahead of print)
T1–3*, N0-3,M0 invasive breast cancer surgically removed within 1 year  Radiotherapy, chemotherapy**, endocrine therapy, trastuzumab, biologics, bisphosphonates

* If pT1C, ≥ 1 adverse prognostic factor
** CXT must be completed

### Primary Outcome:
Invasive cancer free survival

### Secondary Outcome:
Overall survival, Distant Disease-Free Survival, Breast Cancer Free Interval, Adverse Events, Hospitalization (CV, diabetes), QOL (888 subjects)

### Embedded Correlative:
Weight, Fasting Insulin (baseline, 6 months, 5 years), Tumor Blocks

### Sample Size:
3,582 (431 events) – 5 year IDFS 0.85 (placebo), HR =0.76, α=0.05  β=0.20
2 interim analyses (benefit, futility) at 144 and 288 events
Planned subset analyses (α=0.10, 2 sided; β=0.80) in ER/PgR neg (HR 0.65) and Triple negative (HR 0.55)
Targeting a Weakness in Tumor DNA Repair
## Synthetic Lethality

Mutation of either gene alone is compatible with viability, but mutation in both leads to death

<table>
<thead>
<tr>
<th>Gene X</th>
<th>Gene Y</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>No effect</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>No effect</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>No effect</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>Death</td>
</tr>
</tbody>
</table>

PARP Inhibitor Mechanism of Action

1. **PLATINUM CHEMOTHERAPY**
   - Inflicts DNA damage via adducts and DNA crosslinking

2. **PARP1 UPREGULATION**
   - Base-excision repair of DNA damage

3. **INHIBITION OF PARP1**
   - Disables DNA base-excision repair

4. **REPLICATION FORK COLLAPSE**
   - Double strand DNA break

CELL SURVIVAL

CELL DEATH

BRCA1

BRCA2

BSI-201
BRCA1 and BRCA2 -/- Cells Are Very Sensitive to PARP Inhibition

Increased levels of chromosomal aberrations in PARP inhibitor–treated BRCA2 -/- cells

Personal communication, Alan Ashworth
OS – GC

(n = 258)

GCI – GC

(n = 261)

HR

P Value

Median

OS

11.1 mos

11.8 mos

0.88

0.28

Phase II Study: Oral Olaparib, PARP1 Inhibitor in BRCA-Deficient Advanced Breast Cancer

- 54 patients with BRCA1/2 advanced breast cancer
- Refractory to chemotherapy
- 26 patients with evaluable disease
  - ORR: 38% (9/24)
  - 1 complete response

The Genomic Era
The $1000 Genome is Almost Here
Basal-like subtype

1. ~75% of Triple-Negative Breast Cancers (i.e. tumors lacking ER, PgR, and HER2)

Keratin 5/6
Triple Negative: 6 Subtypes and Counting

TNBC: Genomic Chaos

Oncology as Whack-a-Mole

Rapid emergence of compensatory mechanisms of resistance
Multi-platform PIK3CA Pathway Analysis (390 tumors)
TCGA et al., Nature 2012 (PMID 23000897)

Luminal A  Luminal B  HER2E  Basal-like

PIK3CA mutation
PTEN LOH
INPP4B LOH
PTEN copy
INPP4B copy
PIK3CA copy
pAkt 308
pAkt 473
pmTOR
pGSK3
p70S6Kp389
pS6 240.244
p4EBP1 65
INPP4B
PTEN
RPPA (protein)
Saal (mRNA)
CMap (mRNA)
Majumder (mRNA)

* correlated with PI3K protein signature (P<0.0005)
X differences by PTEN/INPP4B LOH (P<0.05)
+ differences by basal subtype vs others (P<0.01)
Thank You