Triple-Negative Breast Cancer

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Betsy Bramsen Professor of Breast Oncology
Director, Maggie Daley Center for Women’s Cancer Care
Tokyo, 2012
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 inhibitors: ENMD 2076
- EGF inhibitors: erlotinib (+metformin,), apatanib
- MEK inhibitors: GSK1120212
- Wnt inhibitor: LGK974
- CDK inhibitor: Dinaciclib, P276-00
- FMS-Kit inhibitor: PLX3397
- Apoptosis 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


- **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; Ann Vanderplas, MS; Melissa E. Hughes, MSc; Richard L. Theriault, DO, MBA; Stephen B. Edge, MD, FACS; Yu-Ning Wong, MD, MSCE; Douglas W. Blayney, MD; Joyce C. Niland, PhD; Eric P. Winer, MD; and Jane C. Weeks, MD, MSc

<table>
<thead>
<tr>
<th>Site</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional vs other</td>
<td>1.32 (1.01-1.74)</td>
<td>.045</td>
<td>1.12 (0.83-1.51)</td>
<td>.45</td>
</tr>
<tr>
<td>Lung vs other</td>
<td>2.17 (1.47-3.21)</td>
<td>&lt;.001</td>
<td>1.73 (1.13-2.66)</td>
<td>.012</td>
</tr>
<tr>
<td>Brain vs other</td>
<td>3.50 (2.10-5.85)</td>
<td>&lt;.001</td>
<td>3.97 (2.35-6.72)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bone vs other</td>
<td>0.26 (0.19-0.36)</td>
<td>&lt;.001</td>
<td>0.39 (0.29-0.54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Liver vs other</td>
<td>1.09 (0.74-1.61)</td>
<td>.67</td>
<td>1.58 (1.07-2.33)</td>
<td>.02</td>
</tr>
</tbody>
</table>

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

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

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)

Intrinsic subtype distribution among Vanderbilt TNBC subtypes

“Intrinsic” Subtypes

- Luminal B
- Luminal A
- Normal Breast-like
- HER2
- Basal-like
- Unclassified
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

- 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

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.
There Are Good Prognosis TNBC

T1a-bN0, untreated
Distant RFS at 5 y

Ok to \textbf{not} treat small, node negative TNBC.

Gonzalez-Angulo et al, JCO 2009
# Molecular Subtypes and Standard Chemotherapy

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

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

*Adapted from Cheang, SABCS 2011*

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**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.

- "BRCAAness" = shared characteristics with sporadic basal-like.

- If there are therapeutic implications of BRCA1 loss, does this include sporadic basal-like?

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"BRCAAness"
- 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

#1 – Chemotherapy choices:
- Platinum agents damage DNA.
- Evidence:
  - Neoadjuvant pCR to cisplatin in known BRCA1+ = 83%

#2 – Exploiting DNA damage response:
- When DNA repair is already impaired, this is an opportunity...PARP inhibition

Yarden and Papa, Mol Cell Ther 2006

Byrski, JCO 2010
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
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

- 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?

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

Platinums and DNA-damaging chemotherapy:
- Promising in BRCA-associated
- Unclear in sporadic TNBC

CALGB 40603
N=400 ER/PR/HER2-Stage II-IIIB

Paclitaxel ± Carboplatin

Dose-dense AC

RT prn

Mandatory research biopsies

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent</th>
<th>No.</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garber et al.</td>
<td>Cisplatin 75 mg/m² q 3 wks x 4</td>
<td>22</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>JCO 2009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baselga</td>
<td>Ixabepilone 100 mg/m² q3 wks x 4</td>
<td>42</td>
<td>11 (26%)</td>
</tr>
<tr>
<td>JCO 2009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin</td>
<td>Doxorubicin 75 mg/m² q 3wks x 4</td>
<td>20</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>ASCO 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Docetaxel 100 mg/m² q 3 wks x 4</td>
<td>28</td>
<td>8 (27%)</td>
</tr>
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<td></td>
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</tbody>
</table>
Proposed Phase II-III ECOG Neoadjuvant Trial in TNBC
Study Chair: Melinda Telli, MD

Candidate of Neoadjuvant Chemotherapy

Randomize/Stratify
- HRD Assay
- BRCA Mutation Status

Sequential AC-weekly paclitaxel
Carboplatin plus gemcitabine
PARP Inhibition in TNBC

Phase II olaparib in BRCA+ and TNBC:

* BRCA1/2-associated

PARP Inhibition
- Promising in BRCA-associated
- Unclear in sporadic TNBC

Phase II veliparib + temozolamid:

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:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>PFS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 2100</td>
<td>Paclitaxel + bevacizumab</td>
<td>0.53 (0.41-0.70)</td>
</tr>
<tr>
<td>AVADO</td>
<td>Docetaxel + bevacizumab</td>
<td>0.68 (NR~1.00)</td>
</tr>
<tr>
<td>RIBBON-1</td>
<td>Chemotherapy + bevacizumab</td>
<td>0.72 (0.49-1.06)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>chemo + bevacizumab</td>
<td>OS HR = 0.96 (0.79-1.16)</td>
</tr>
</tbody>
</table>

### Neoadjuvant trials:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>pCR HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeparQuinto</td>
<td>EC-docetaxel + bevacizumab</td>
<td>1.67 (*)(1.00 in HR+ subset)</td>
</tr>
<tr>
<td>NSABP B-40</td>
<td>chemo + bevacizumab</td>
<td>&lt;1.2 (ns) (*significant in HR+ subset)</td>
</tr>
</tbody>
</table>

*O’Shaughnessy, ASCO’11; Von Minckwitz, NEJM’12; Bear, NEJM’12*
Theory #3: Targeting Heterogeneity of TNBC

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

Lehmann et al, JCI 2011
TBCRC 011: Bicalutamide in AR+ TNBC

Consented for AR testing (n=452)

Screened for AR expression (n=424)

AR(+) (n=51)

On study (n=28)

Eligible on study (n=26)

Ineligible for testing (n=28)

AR(-) (n=373)

Ineligible for therapy (n=8)

Eligible for therapy; trial closed to accrual (n=15)

Ineligible post therapy (n=2)

Clinical Benefit Rate = 21% (95% CI 7.1-42.1%)

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**

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>P+B</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>17%</td>
<td>34%</td>
</tr>
<tr>
<td>Measurable (79%)</td>
<td>17%</td>
<td>41%</td>
</tr>
</tbody>
</table>

**ER and/or PR Positive**

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>P+B</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>23%</td>
<td>37%</td>
</tr>
<tr>
<td>Measurable (46%)</td>
<td>30%</td>
<td>51%</td>
</tr>
</tbody>
</table>
Targeting EGFR
BALI-1

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

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Cisplatinum + Cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1.7%</td>
<td>1.7%</td>
</tr>
<tr>
<td>PR</td>
<td>8.6%</td>
<td>18.3%</td>
</tr>
<tr>
<td>ORR</td>
<td>10.3% [3.9-21.2%]</td>
<td>20.0% [13.1-28.0%]</td>
</tr>
<tr>
<td>PFS (clinical)</td>
<td>1.5 mos</td>
<td>3.1 mos</td>
</tr>
<tr>
<td>PFS (radiographic)</td>
<td>1.5 mos</td>
<td>3.7 mos</td>
</tr>
</tbody>
</table>

Some improvement but not enough. Needs selection strategy.

Baselga, ESMO 2010
## Randomized Trials of Cetuximab in Triple Negative Metastatic Breast Cancer

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

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