Progress in Treating Advanced Triple Negative Breast Cancer

Lisa A. Carey, M.D.
University of North Carolina at Chapel Hill
Lineberger Comprehensive Cancer Center
Triple Negative Breast Cancer by Subtype

Defined by clinical assays:
- ER- PR- HER2-

Molecular assays:
- 3/4 molecularly “appropriate”
- 1/4 are not what they seem
Theory #1: Chemotherapy Can Be (Should Be?) Tailored
“BRCAAness” = Characteristic of BRCA+

- 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
## Platinum Responsiveness in TNBC

### Table 1: Summary of completed neoadjuvant chemotherapy trials.*

<table>
<thead>
<tr>
<th>Clinical trials</th>
<th>Design</th>
<th>Drugs</th>
<th>Population</th>
<th>pCR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver et al. [12]</td>
<td>Phase II single arm</td>
<td>Cisplatin × 4</td>
<td>TNBC</td>
<td>6/28 (21%)</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Byrski et al. [13]</td>
<td>Retrosp.</td>
<td>All; CMF; AD; AC/FAC; cisplatin</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>BRCA1 mut.</strong></td>
</tr>
<tr>
<td>Bear et al. [14]</td>
<td>Phase III random.</td>
<td>Arm 1A: D × 4 → AC × 4 Arm 1B: D + X × 4 → AC × 4 Arm 1C: D + G × 4 cycles → Ac × 4</td>
<td>HER2−</td>
<td>Arm 1A: 102/393 (26%) Arm 1B: 91/390 (23%) Arm 1C: 106/388 (27%)</td>
</tr>
<tr>
<td>Zelnak et al. [16]</td>
<td>Phase II random.</td>
<td>Arm A: D × 4 cycles → X × 4; Arm B: D + X × 8 cycles.</td>
<td>HER2−</td>
<td>Arm A: 2/25 (8%) Arm B: 3/26 (12%) Arm A/B (TNBC): 4/21 (19%)</td>
</tr>
<tr>
<td>Huober et al. [18]</td>
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</tr>
<tr>
<td>Baselga et al. [19]</td>
<td>Phase II single arm</td>
<td>Ixabepilone × 4</td>
<td>Any breast cancer</td>
<td>TNBC: 11/42 (26%) Non-TNBC: 18/119 (15%)</td>
</tr>
</tbody>
</table>

*All: 24/102 (24%) CMF: 1/14 (7%) AD: 2/25 (8%) AC/FAC: 11/51 (22%) Cisplatin: 10/12 (83%)
Non-BRCA1 TNBC and Platinums in Stage IV?

<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

Baselga, ESMO’10; O’Shaughnessy, ASCO’11; Carey et al, JCO’12; Isakoff, ASCO’11
**First-Line Chemotherapy**

**CALGB 40502/NCCTG N063H**

Randomized Phase III Trial of Weekly Paclitaxel compared to Weekly Nanoparticle Albumin Bound Nab-Paclitaxel or Ixabepilone +/- Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

N = 799
Untreated Stage IV

Strata: Adj taxanes ER/PR status

Randomize 1:1:

Nab-paclitaxel 150 mg/m² weekly + bevacizumab 10 mg/kg q 2 wks

Paclitaxel 90 mg/m² weekly + bevacizumab 10 mg/kg q 2 wks

Ixabepilone 16 mg/m² weekly + bevacizumab 10 mg/kg q 2 wks

Restage q 2 cycles until disease progression

Rugo H et al, ASCO 2012
CALGB 40502 Subset Analyses

**Triple Negative Disease**

- **40502 overall findings:**
  - Weekly paclitaxel > ixabepilone
  - Weekly paclitaxel less toxic than either (in general)

- **TNBC Subset:**
  - No real difference from parent trial
  - 98% received bevacizumab

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab vs. pac</td>
<td>0.93</td>
<td>0.7354</td>
<td>0.62 – 1.40</td>
</tr>
<tr>
<td>ixa vs. pac</td>
<td>1.46</td>
<td>0.0647</td>
<td>0.98 – 2.18</td>
</tr>
</tbody>
</table>
Later Lines of Therapy?

A Phase III, Open-Label, Randomized, Multicenter Study Of Eribulin Mesylate Versus Capecitabine In Patients With Locally Advanced Or Metastatic Breast Cancer Previously Treated With Anthracyclines And Taxanes

Patients (N=1102)
Locally advanced or MBC
- ≤3 prior chemotherapy regimens (≤2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

Eribulin mesylate
1.4 mg/m²† 2- to 5-min IV
Day 1 & 8 q21 days

Capecitabine
1250 mg/m² BID orally
Days 1-14, q21 days

Randomization 1:1

Co-primary endpoint
- OS and PFS

Secondary endpoints
- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribulin arm only)

Kaufmann P et al, SABCS 2012
Eribulin Vs. Capecitabine

- Eribulin = capecitabine in 2nd+ line therapy
- Very different toxicity profiles:
  - Eribulin: neutropenia, alopecia, neuropathy
  - Capecitabine: HFS, diarrhea

Kaufmann P et al, SABCS 2012
Theory #2: Antiangiogenic Drugs

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

Hu et al, BMC Medicine 2009
### Bevacizumab in Triple Negative: Stage IV Setting

#### First-line randomized phase III trials:

<table>
<thead>
<tr>
<th>Stage IV Trial</th>
<th>Regimen</th>
<th>DFS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 2100</td>
<td>Weekly 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>
</tbody>
</table>

**However…**

<table>
<thead>
<tr>
<th>Meta-analysis 3 first-line studies chemo + bevacizumab</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.96 (0.79-1.16)</td>
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</table>

#### RIBBON-2 randomized phase III trial, pretreated:

<table>
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<tr>
<th>TNBC subset</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>chemo + bevacizumab</td>
<td>PFS 0.494 (0.33–0.74)</td>
</tr>
<tr>
<td>* exploratory</td>
<td>OS 0.624 (0.39–1.007)</td>
</tr>
</tbody>
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O'Shaughnessy J et al, ASCO 2011; Bruisky BCRT 2012
Theory #3: BRCA1 Loss is Targetable

Exploiting DNA damage response:

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

Yarden and Papa, Mol Cell Ther 2006
DNA damage happens.
• Naturally occurring
• Induced e.g. chemo, radiation

Several repair options:
• BRCA1/2 dependent
• PARP dependent

When BRCA1 or 2 is damaged, cell becomes dependent on other repair mechanisms.

PARP inhibitors exploit this Achilles’ heel.

Ellisen, Cancer Cell 2011; Tutt et al, Lancet 2010
## Olaparib in BRCA1/2 Carriers: Results

<table>
<thead>
<tr>
<th>Intent-to-treat cohort</th>
<th>Olaparib 400 mg bid (n=27)</th>
<th>Olaparib 100 mg bid (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate, n (%)</td>
<td><strong>11 (41)</strong>*</td>
<td>6 (22)*</td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response, n (%)</td>
<td>10 (37)</td>
<td>6 (22)</td>
</tr>
</tbody>
</table>

Toxicity included:
- fatigue (56%) nausea/vomiting (<40%), headache (37%) – mostly mild/moderate
- 30% reduced doses, 30% delayed doses for toxicity

*Tutt A et al, Lancet Oncol 2009*
Breast Cancer, Ovarian Cancer and PARPi

• Non-BRCA ovarian cancer responds to olaparib...Evidence of BRCAness.

• Not seen with non-BRCA breast cancer.
  – Triple negative

Gelmon K et al, Lancet Oncol 2011
Phase II Veliparib (ABT-888) + Temozolamide

- Response rate = 7%
- ONLY in BRCA1/2+ (RR 38%)
- * = BRCA carriers

* = BRCA carriers

BRCA carriers: Median PFS = 5.5 Mo
Noncarriers: PFS = 1.8 Mo

p-value = 0.0042

Isakoff et al, ASCO 2011

Phase I Veliparib + oral Cyclophosphamide

- Phase I dose escalation. Mixed tumor types.
- 7/35 partial responses
  - 6/13 BRCA1/2+

Kummar et al, Clin Cancer Res 2012
Theory #4: 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
What we know:

- TNBC is heterogeneous
- Chemotherapy is mainstay and (at the moment) is the same as for other subtypes.
  - First-line taxanes appropriate
  - Second+ lines: add eribulin to other options

BRCA1-associated TNBC may be different:

- Platinums
- PARP inhibition

Is TNBC where individualized therapy will start?
Thanks to My UNC Colleagues!