The elements & clinical care of triple-negative breast cancer

Melinda Telli, M.D.

Stanford University School of Medicine
Outline

- Clinical features of triple-negative breast cancer
- Treatment implications of germline BRCA1 & BRCA2 mutations in TNBC
- Update on platinum in BRCA+ and sporadic TNBC
- Emerging concepts in immunotherapy
Triple-Negative Breast Cancer

Current Status

- Standard treatment for early-stage TNBC in 2014 consists of combination chemotherapy
  - Anthracycline and taxane-based
  - Has not changed significantly in 10++ years

- Selective use and targeting of available cytotoxics not optimized
  - Starting to see changes here!

- Germline BRCA1/2 status generally not reported in trials
  - Important to truly understand results in this disease
Triple-Negative Breast Cancer

- 13% of all breast cancer in California
  - California Cancer Registry 1999-2005; n=87,604

- Varies by ethnicity/race
  - White: 11%
  - Japanese: 11%
  - Chinese: 11%
  - Black: 26%
  - Hispanic: 17%

- Disproportionately affects the young (<40)

Early risk of recurrence

Sites of First Distant Recurrence

- **Triple-negative cancer**
  - Brain: 30%
  - Lung: 40%
  - Liver: 20%
  - Bones: 10%

- **Non-triple-negative cancer**
  - Brain: 10% (higher in HER2+ breast cancer)
  - Lung: 20%
  - Liver: 30%
  - Bones: 40%
Most triple-negative breast cancers are ‘basal-like’ by gene expression.
Intrinsic Subtype Distribution Among Clinically Triple-Negative Breast Cancers

73% Basal
17% HER2-enriched
5% LumB
2% LumA
3% Normal

PAM50

Cheang M, et al. ASCO 2012
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

Adapted from Lehmann et al; excludes 62 unclassified cases

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 and cytokine signaling (overlap with medullary breast cancer gene 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 genes associated with stem cells

**Luminal androgen receptor (LAR):** Enriched in hormonally-regulated pathways, androgen receptor signaling. Displays luminal expression patterns (molecular apocrine carcinomas)

Copyright © 2011, American Society for Clinical Investigation
Targeting the androgen receptor (AR) in women with AR+ ER-/PR- metastatic breast cancer

ER/PR(-) (IHC ≤10%) LABC/MBC

Measurable/ non-measurable
No limit to prior therapy

AR testing
Central testing at MSKCC*

AR(+) IHC >10%

Bicalutamide 150mg daily
1 cycle = 4 weeks

Toxicity evaluation every 4 weeks (± 5 days)
Response evaluation by RECIST every 12 weeks (± 2 weeks)

*AR tested using primary antibody AR 441 (Dako; dilution: 1:300)

Gucalp A, et al., Clin Cancer Research 2013
### Results: Patients with Clinical Benefit (5/24 = 21%)

<table>
<thead>
<tr>
<th>Patients with clinical benefit on bicalutamide</th>
<th>AR%</th>
<th>ER%</th>
<th>PR%</th>
<th>HER2</th>
<th>Site of Testing</th>
<th>Site of Mets</th>
<th>Prior Therapy MBC/LABC</th>
<th>DOR on Prior Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>10-20</td>
<td>1</td>
<td>0</td>
<td>Neg</td>
<td>1&lt;sup&gt;0&lt;/sup&gt;</td>
<td>LN</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>#2</td>
<td>&gt;80</td>
<td>3</td>
<td>0</td>
<td>Neg</td>
<td>Met</td>
<td>GI</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>#3</td>
<td>&gt;80</td>
<td>0</td>
<td>0</td>
<td>+/-</td>
<td>1&lt;sup&gt;0&lt;/sup&gt;</td>
<td>Breast, LN</td>
<td>1</td>
<td>NR</td>
</tr>
<tr>
<td>#4</td>
<td>&gt;90</td>
<td>0</td>
<td>0</td>
<td>Neg</td>
<td>1&lt;sup&gt;0&lt;/sup&gt;</td>
<td>LN, Bone</td>
<td>1</td>
<td>158wk</td>
</tr>
<tr>
<td>#5</td>
<td>&gt;50</td>
<td>0</td>
<td>0</td>
<td>Neg</td>
<td>1&lt;sup&gt;0&lt;/sup&gt;</td>
<td>LN, Bone</td>
<td>1</td>
<td>15 wk</td>
</tr>
</tbody>
</table>

DOR duration of response; NA not applicable; NR no response

Gucalp A, et al., Clin Cancer Research 2013
The search for a target:
Clues from cancer genetics
Hereditary Breast and Ovarian Cancer

- Most hereditary breast and ovarian cancers are due to germline BRCA1 and BRCA2 mutations
- BRCA1/2-associated cancers are compromised in DNA repair
Association between TNBC & germline mutations in BRCA1/2

- Approximately 75-80% of BRCA1 mutation-associated breast cancers are basal-like by gene expression or IHC \(^1,2\)

- In unselected TNBC, frequency of BRCA1/2 mutations reported to be up to 19.5%\(^3\)

Homologous recombination defects in breast cancer

- HR deficiency characterizes breast cancers in **BRCA1/2 mutation carriers**
  - Due to loss of heterozygosity at BRCA1 or BRCA2

- HR deficiency implicated in **sporadic TNBC**
  - Methylation
  - Somatic mutation
  - Other epigenetic mechanisms

Twenty years on from the cloning of BRCA1

Potential of individualizing systemic treatment based on germline BRCA1/2 status not yet realized

- BRCA1/2 germline status currently does NOT factor into systemic therapy decisions

- PARP inhibitors have single agent activity in advanced BRCA1/2 mutation-associated breast cancer
  - NO DRUGS FDA APPROVED

- Responses to standard chemotherapy drugs in carriers not well characterized
  - NO DETERMINATION OF BRCA1/2 STATUS IN MOST MAJOR THERAPEUTIC TRIALS, EVEN IN TNBC
Should we use BRCA1/2 mutation status as a biomarker for treatment selection?

- Strong pre-clinical and early clinical data suggesting high level activity of DNA repair targeted therapeutics

- BRCA1/2-deficient breast tumors exhibit differential chemosensitivity compared to BRCA1/2-proficient cancers\(^1-3\)
  - Greater sensitivity to platinum, doxorubicin, gemcitabine
  - Less sensitivity to taxanes
  - Single agent sensitivity to PARP inhibitors


My vote is yes
PARP1/2 Function

- Key enzymes involved in repair of single strand DNA breaks

- PARP is required for the repair of oxidative DNA damage-associated DNA breaks via base excision repair (BER)
BRCA1 and 2 deficient cells are markedly sensitive to inhibition of PARP

Loss of BRCA + Loss of PARP1 = “Synthetic Lethal” Interaction

PARP inhibitors in advanced BRCA mutant breast cancer: *Initial proof-of-concept*

**Olaparib: Superior activity at higher dose**

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 400 mg twice daily (n=27)</th>
<th>Olaparib 100 mg twice daily (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>11 (41%; 25–59)</td>
<td>6 (22%; 11–41)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (4%; 1–18)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>10 (37%; 22–56)</td>
<td>6 (22%; 11–41)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12 (44%; 28–63)</td>
<td>12 (44%; 28–63)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4 (15%; 6–32)</td>
<td>9 (33%; 19–53)</td>
</tr>
</tbody>
</table>

Data are number (%; 95% CI).

---

Tutt A. Lancet. Published online July 6, 2010
PARP inhibitor development in BRCA1/2 mutation-associated breast cancer

- No FDA approved agents at present... STILL!
  - Has been difficult for patients to access these drugs despite encouraging data in the heavily pre-treated setting

- Failure of the phase 3 iniparib study in mTNBC dampened enthusiasm
  - Realization that this drug was not a bone fide PARP inhibitor did not help

- Recent increase in randomized clinical trials in BRCA1/2 mutant breast cancer
  - Combination chemotherapy +/- PARP inhibitor
  - Multiple newer studies of single agent PARP inhibitor versus treatment-of-physician’s choice

- Role of PARP inhibition in sporadic TNBC remains undefined
# PARP inhibitors in advanced clinical development for BRCA1/2+ metastatic breast cancer

<table>
<thead>
<tr>
<th>Compound</th>
<th>Other names</th>
<th>Phase of testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib (AbbVie)</td>
<td>ABT-888</td>
<td>Large Phase II nearing completion (211/255 enrolled)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III (upcoming)</td>
</tr>
<tr>
<td>Olaparib (AstraZeneca)</td>
<td>KU0059436, AZD2281</td>
<td>III (Not yet open in U.S.)</td>
</tr>
<tr>
<td>Niraparib (Tesaro)</td>
<td>MK4827</td>
<td>III ongoing</td>
</tr>
<tr>
<td>BMN-673 (BioMarin)</td>
<td></td>
<td>III ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase II in previously platinum-treated ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase II for other hereditary mutations upcoming</td>
</tr>
</tbody>
</table>
Platinum in triple-negative breast cancer
Platinum

- Cisplatin first approved by the FDA in 1978
  - Noted to have activity in metastatic breast cancer
- Family of platinum salts bind directly to DNA
  - Results in formation of DNA-platinum adducts and consequently intra- and inter-strand DNA crosslinks that impede cell division
- Recent renewed interest in investigating the role of platinum chemotherapy in breast cancer
  - Hypothesis of greater susceptibility of TN and BRCA1/2 mutant BC to DNA damaging chemotherapeutic agents
  - Limited data in metastatic disease; most important insights from neoadjuvant setting

Platinum in BRCA1/2 mutant breast cancer

- Proof-of-concept neoadjuvant study of 25 BRCA1 mutation carriers (80% TNBC)\(^1\)
  - **pCR rate of 72%** with single agent cisplatin 75 mg/m\(^2\) every 21 days x 4

- Rate of pCR to standard anthracycline/taxane-based therapy in BRCA1/2 carriers not well known
  - Retrospective data from USA: **pCR of 37% versus 31%** in BRCA1/2 positive vs. negative TNBC pts treated with AC +/-T\(^2\)
  - Retrospective data from Israel: **pCR of 67% vs. 37%** in BRCA1/2 positive vs. negative TNBC treated with AC-T dose dense

Randomized phase II neoadjuvant “add-on” carboplatin studies in unselected TNBC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Regimen</th>
<th>pCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba</td>
<td>94</td>
<td><strong>Epirubicin</strong> 90 mg/m2 + <strong>cyclophosphamide</strong> 600 mg/m2 q21 days x 4 cycles followed by <strong>docetaxel</strong> 100mg/m2 q21 days x 4 or <strong>docetaxel</strong> 75 mg/m2 + <strong>carboplatin</strong> AUC 6 every 21 days x 4 cycles</td>
<td>30% with Cp</td>
</tr>
<tr>
<td><strong>GEICAM 2006-03</strong></td>
<td></td>
<td>30% no Cp</td>
<td></td>
</tr>
<tr>
<td>von Minckwitz</td>
<td>315</td>
<td><strong>Paclitaxel</strong> 80 mg/m2 every 7 days + <strong>non-pegylated liposomal doxorubicin</strong> 20 mg/m2 every 7 days + <strong>bevacizumab</strong> 15 mg/kg IV every 21 days +/- <strong>carboplatin</strong> AUC 1.5 every 7 days x 18 cycles</td>
<td>53% with Cp</td>
</tr>
<tr>
<td><strong>GeparSixto</strong></td>
<td></td>
<td>37% no Cp</td>
<td></td>
</tr>
<tr>
<td>Sikov</td>
<td>443</td>
<td><strong>Paclitaxel</strong> 80 mg/m2 every 7 days x 12 cycles followed by <strong>doxorubicin</strong> 60 mg/m2 + <strong>cyclophosphamide</strong> 600 mg/m2 every 2 weeks x 4 cycles +/- <strong>carboplatin</strong> AUC 6 every 21 days x 4 cycles (with paclitaxel) +/- <strong>bevacizumab</strong> 10 mg/kg every 2 weeks x 9 cycles (with paclitaxel and doxorubicin/cyclophosphamide)</td>
<td>54% with Cp</td>
</tr>
<tr>
<td><strong>CALGB 40603</strong></td>
<td></td>
<td>41% no Cp</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>52% with Bev</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>44% no Bev</strong></td>
<td></td>
</tr>
</tbody>
</table>
A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto – GBG 66)


for the GBG/AGO-B study groups

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.
**Therapy in TNBC subgroup**

- **N=315 centrally confirmed TNBC**
- **PM**
  - Paclitaxel 80 mg/m² q1w
  - Non-pegylated liposomal doxorubicin 20 mg/m² q1w
  - Carboplatin AUC 1.5-2* q1w

- **PMCb**

- **R**

**TNBC:** Bevacizumab 15 mg/kg q3w

von Minckwitz et al. Lancet Oncology, May 2014
pCR Rates Overall and in TNBC Subgroup

ypT0 ypN0

Overall

<table>
<thead>
<tr>
<th>Group</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>1.33 (0.96-1.85)</td>
<td>0.107*</td>
</tr>
<tr>
<td>PMCb</td>
<td>36.9%</td>
<td>43.7%</td>
</tr>
</tbody>
</table>

**TNBC**

<table>
<thead>
<tr>
<th>Group</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>1.94 (1.24 – 3.04)</td>
<td>0.005</td>
</tr>
<tr>
<td>PMCb</td>
<td>36.9%</td>
<td>53.2%</td>
</tr>
</tbody>
</table>

*Phase II significance level < 0.02

von Minckwitz et al. Lancet Oncology, May 2014

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.
Discontinuations common and primarily due to adverse events

<table>
<thead>
<tr>
<th></th>
<th>PM</th>
<th>PMCb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>299</td>
<td>296</td>
</tr>
<tr>
<td>Started treatment</td>
<td>293</td>
<td>295</td>
</tr>
<tr>
<td>Discontinued all treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adverse event</td>
<td>31.5</td>
<td>37.7</td>
</tr>
<tr>
<td>investigator‘s decision</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>patient’s wish</td>
<td>3.5</td>
<td>5.2</td>
</tr>
<tr>
<td>progressive disease</td>
<td>0.7</td>
<td>1.7</td>
</tr>
<tr>
<td>death*</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Completed 6 cycles of treatment</td>
<td>60.9</td>
<td>52.2</td>
</tr>
</tbody>
</table>

*PM: TNBC: acute myocardial infarction (1), febrile neutropenia (1); HER2+: asystole (1), pneumonia (1)
PMC: TNBC: sepsis after port infection (1)

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.
Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant weekly paclitaxel followed by dose-dense AC on pathologic complete response rates in triple-negative breast cancer: CALGB/Alliance 40603

CALGB 40603: Schema – Randomized Phase II

Paclitaxel 80 mg/m\(^2\) wkly x 12  
ddAC x 4

Bevacizumab 10 mg/kg q2wks x 9

Paclitaxel 80 mg/m\(^2\) wkly x 12  
ddAC x 4

Carboplatin AUC 6 q3wks x 4

Paclitaxel 80 mg/m\(^2\) wkly x 12  
ddAC x 4

Carboplatin AUC 6 q3wks x 4

Bevacizumab 10 mg/kg q2wks x 9
pCR Breast/Axilla (ypT0/is N0)

**+/- Carboplatin**

- **N=212**
  - 41% (35-48%)
  - 54% (48-61%)
  - Odds ratio: 1.71
  - p = 0.0029

**+/- Bevacizumab**

- **N=221**
  - 44% (38-51%)
  - 52% (45-58%)
  - Odds ratio: 1.36
  - p = 0.0570

This presentation is the intellectual property of William Sikov, MD. Contact at wsikov@lifespan.org for permission to reprint or distribute.
Recent TNBC platinum data in context

- Two recent P2 randomized carboplatin studies positive
  - GEICAM / 2006-03 negative

- GeparSixto and CALGB 40603 show increase in pCR with carboplatin
  - In both studies, bevacizumab was also included

- In the randomized phase III GeparQuinto trial, bevacizumab increased pCR in the TNBC subset
  - EC-Docetaxel: pCR = 27.9%  Δ11.4%
  - EC-Docetaxel + Bev pCR = 39.3%

- Looking at individual arms in CALGB 40603
  - T-AC  pCR 39%  Δ10%
  - TCp-AC  pCR 49%  Δ11%
  - TCpB-ACB  pCR 60%  Δ11%
Recent TNBC platinum data in context

- We know bevacizumab increases pCR by ~10%, but does **not** add benefit in adjuvant TNBC treatment
  - Phase III BEATRICE study showed no improvement in DFS or OS with adjuvant bevacizumab in TNBC

- Need to consider the chance that platinum (like bev) will not add DFS/OS benefit in a definitive phase III carboplatin TNBC trial
  - Additive toxicity also a significant concern

- Highlights need for **biomarkers of platinum response**
  - Candidates: Germline BRCA mutation status
    - ‘Genomic scar’ due to HR defects
    - Tumor lymphocytic infiltration
Pathological complete response (pCR) rates after carboplatin-containing neoadjuvant chemotherapy in patients with germline BRCA (gBRCA) mutation and triple negative breast cancer (TNBC) – Results from GeparSixto

Abstract # 1005

Gunter von Minckwitz, Eric Hahnen, Peter A. Fasching, Jan Hauke, Andreas Schneeweiss, Christoph T. Salat, Mahdi Rezai, Jens U. Blohmer, Dirk M. Zahm, Christian Jackisch, Bernd Gerber, Peter Klare, Sherko Kümmel, Holger Eidtmann, Stephan Paepke, Valentina Nekljudova, Sibylle Loibl, Michael Untch, Rita Schmutzler for the GBG/AGO-B study groups

Presented at the 2014 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.
GeparSixto: BRCA1/2 & RAD mutation carriers achieve superior pCR rates

- Germline blood was available for 294 of 315 TNBC pts
  - BRCA1/2 mutations were detected in 41 patients using a number of methods
  - RAD50/RAD51c mutations were detected in 3 patients
  - 164 patients incompletely genotyped

- Considering all randomized patients with TNBC (n=294)
  - pCR among B1/2 + RAD carriers = 54.5%
  - pCR among B1/2 + RAD non-carriers = 41.6%
    \[ \Delta 12.9\%; \ p=0.11 \]
  - pCR among B1/2 + RAD non-carriers with +FH = 44.3%
  - pCR among B1/2 + RAD non-carriers with no FH = 40.4%
    \[ \Delta 3.9\% \]

von Minckwitz et al. ASCO 2014, abstract 1005
## Platinum response by family history & germline HR pathway mutation status

<table>
<thead>
<tr>
<th></th>
<th>PM (N=146)</th>
<th>PMCb (N=149)</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% pCR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No family history</td>
<td>34.5</td>
<td>46.0</td>
<td>1.61</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Δ 11.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of BC/OC</td>
<td>30.8</td>
<td>57.5</td>
<td>3.04</td>
<td>0.02</td>
</tr>
<tr>
<td>without mutation (n=79)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Δ 26.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gBRCA/RAD mutation</td>
<td>43.5</td>
<td>66.7</td>
<td>2.60</td>
<td>0.13</td>
</tr>
<tr>
<td>with/without family history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Δ 23.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

von Minckwitz et al. ASCO 2014, abstract 1005
Carboplatin benefit among those with FH *lacking* a germline B1/2 or RAD mutation fascinating

- Due to as yet undiscovered BRCA1/2 mutations?
  - >50% yet to have comprehensive B1/2 genotyping

- Due to germline mutations in other homologous recombination DNA repair pathway genes?
  - Excellent opportunity to assess additional HR pathway genes in this trial
Breast Cancer Genes: The Landscape
Additional germline biomarkers?

- Many other genes implicated in familial breast cancer\(^1\)
  - Many in homologous recombination pathway
- In women testing negative for BRCA1/2 mutations
  - Multi-gene sequencing identifies an additional \(~10\%\) with pathogenic germline mutations\(^2\)
- DNA repair-targeted therapy is hypothesized to have a role in these patients with non-B1/2 germline HR alterations

---


**Figure 2.** Breast-Cancer Susceptibility Loci and Genes.
Rise of the germline multiplex panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Ambry Genetics*</th>
<th>University of Washington Laboratory Medicine†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CancerNext</td>
<td>BreastNext</td>
</tr>
<tr>
<td>APC</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>ATM</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>ATR</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>BABAM1</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>BAP1</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>BARD1</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>BRIP1</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>CDH1</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>CDK4</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>CHEK1</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>CHEK2</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>FAM175A/Abraxas</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>MLH1</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>MRE11A</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>MSH2-positive EPCAM</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>MSH6</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>MUTYH</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>NBN</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>PALB2</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>PMS2</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

Identifying cause or consequence:
Which will prove the better biomarker?
PrECOG 0105: Final efficacy results from a phase II study of gemcitabine & carboplatin plus iniparib (BSI-201) as neoadjuvant therapy for triple-negative and BRCA1/2 mutation-associated breast cancer

## Results PrECOG 0105

### Intent-to-treat population

<table>
<thead>
<tr>
<th>Pathologic Response (n=80)</th>
<th>All patients</th>
<th>BRCA 1/2 wild-type</th>
<th>BRCA 1/2 mutant</th>
<th>TN &amp; BRCA 1/2 mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 80</td>
<td>n = 61</td>
<td>n = 19</td>
<td>n = 16</td>
<td></td>
</tr>
<tr>
<td>pCR [RCB 0]; n (%)</td>
<td>29 (36%)</td>
<td>20 (33%)</td>
<td>9* (47%)</td>
<td>9* (56%)</td>
</tr>
<tr>
<td>90% CI</td>
<td>27–46</td>
<td>23–44</td>
<td>27–68</td>
<td>33–77</td>
</tr>
<tr>
<td>RCB 0/1; n (%)</td>
<td>45 (56%)</td>
<td>31 (51%)</td>
<td>14 (74%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>90% CI</td>
<td>46–66</td>
<td>40–62</td>
<td>52–89</td>
<td>52–91</td>
</tr>
</tbody>
</table>

* One BRCA1 carrier had bilateral TNBC & achieved pCR in both breasts
Homologous Recombination Deficiency (HRD) Assay

Goal:
- To detect a genomic HR deficiency ‘footprint’ in a tumor caused by various defects in the HR pathway
  - Potential to identify non-BRCA1/2 mutation carriers with ‘BRCA-like’ cancers who may benefit from DNA repair targeted treatment strategies

Assay development:
- Association of genomic patterns of loss of heterozygosity (LOH) & HR deficiency assessed in ovarian cancer

Major Finding:
- LOH regions of intermediate size were observed more frequently in tumors with defective BRCA1 or BRCA2
  - HRD Score = Count of the # of LOH regions of intermediate size (> 15 Mb and < whole chromosome) observed in the tumor genome

Pathologic response by HRD Score

## Association of HRD Score & Response (n=77)

<table>
<thead>
<tr>
<th></th>
<th>Mean HRD Scores: All patients (n=77)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>16.2</td>
<td>p=0.0003</td>
</tr>
<tr>
<td>Non-responders</td>
<td>11.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean HRD Scores: BRCA1/2 intact (n=58)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>16.6</td>
<td>p=0.0006</td>
</tr>
<tr>
<td>Non-responders</td>
<td>11.1</td>
<td></td>
</tr>
</tbody>
</table>

Correlations between response and clinical stage, grade not significant

Favorable response (RCB 0/1) by HRD Score

<table>
<thead>
<tr>
<th></th>
<th>Proportion of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRD &lt; 10 (n=20)</td>
<td>20</td>
</tr>
<tr>
<td>HRD ≥ 10 (n=57)</td>
<td>70</td>
</tr>
</tbody>
</table>

p = 0.0001

Telli ML, et al. SABCS 2012
Favorable response (RCB 0/1) by HRD Score & BRCA1/2 Status

Telli ML, et al. SABCS 2012
Role of Platinum in Metastatic TNBC
Platinum in metastatic TNBC

- Randomized data comparing platinum to other standard chemotherapies are lacking

- Cross-study comparisons difficult
  - Few TNBC specific trials -> mostly subsets
  - Various “triple-negative” definitions
  - BRCA1/2 genotype largely unassessed
  - TNBC is heterogeneous -> varying chemosensitivity
  - Disease-free interval important in this disease and not always adjusted for in trials
# Platinum in unselected mTNBC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>Prior Chemo (%)</th>
<th>Disease-free interval (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine / Carboplatin(^1)</td>
<td>258</td>
<td>30%</td>
<td>4.1</td>
<td>90%</td>
<td>15 mos</td>
</tr>
<tr>
<td>1(^{st}) line</td>
<td>148</td>
<td></td>
<td>4.6</td>
<td></td>
<td>15.9 mos</td>
</tr>
<tr>
<td>2(^{nd}/3(^{rd}) line</td>
<td>110</td>
<td></td>
<td>2.9</td>
<td></td>
<td>13.8 mos</td>
</tr>
<tr>
<td>Carboplatin or cisplatin(^2)</td>
<td>86</td>
<td>26%</td>
<td>2.9</td>
<td>86%</td>
<td>NA</td>
</tr>
<tr>
<td>1(^{st}) &amp; 2(^{nd}) line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ORR in BRCA1/2 mutant 55% vs. 20% in BRCA1/2 wild-type

2. Isakoff S, et al. ASCO 2014 (abstract 1020)
Triple Negative breast cancer Trial

A randomised phase III trial of carboplatin compared to docetaxel for patients with metastatic or recurrent locally advanced ER-, PR- and HER2- breast cancer.

Incorporating the BRCA Trial

Main REC Reference Number: 07/Q0603/67
EudraCT Number: 2006-004470-26
CRUK Number: CRUK/07/012

ISRCTN: ISRCTN97330959
Protocol Number: ICR-CTSU/2006/10003
CTA Number: 22138/0004/001-0001

Completed Accrual 2014
400 patients
80 UK centres

Dr Andrew Tutt (Chief Investigator)

Andrew Tutt
TNT / BRCA Trial

First Line Advanced TNBC or BRCA1/BRCA2 Breast Cancer

Randomise 1:1

RECIST ORR

TTP

PFS

ORR 2\textsuperscript{nd} line

Toxicity

OS

400 patients

Central ER / PR / HER2 Basal Phenotypes
BRCA1/2 genotype
53BP loss

HR Genome Scar
Somatic BRCA1/2
BRCA1 methylation
Whole Exome NGS
RNA Seq

Recurrence Disease BX
Genome Scars
Reversion Mutations
Whole Exome NGS
RNA Seq

Correlative Biology Program
Emerging concepts in immunotherapy
Association of increased tumor-infiltrating lymphocytes (TILs) with immunomodulatory (IM) triple-negative breast cancer (TNBC) subtype and response to neoadjuvant platinum-based therapy in PrECOG 0105

Abstract 1000

Results: TILs significantly associate with pathologic response by RCB value in multivariate models

<table>
<thead>
<tr>
<th>Covariate</th>
<th>sTILs (p value)</th>
<th>iTILs (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>T size by MRI</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>N stage</td>
<td>NS</td>
<td>0.05</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>gBRCA status</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>sTILs (increase of 10%)</td>
<td><strong>0.02</strong></td>
<td></td>
</tr>
<tr>
<td>iTILs (increase of 10%)</td>
<td></td>
<td><strong>0.009</strong></td>
</tr>
</tbody>
</table>

For every 10% increase in sTILs, there is an expected lowering of 0.17 in RCB value
For every 10% increase in iTILs, there is an expected lowering of 0.50 in RCB value

Multivariate model using pCR:
sTILs were not significant in this model
For every 10% increase in iTILs, there is an expected increase of 162% in the odds of pCR

Presented by: Shaveta Vinayak, M.D., M.S.
Lessons learned from mice (and applied to men)

In Mice …

- Each tumor is immunologically unique.\(^1\),\(^2\)
- One aspect of a tumor’s unique-ness comes from random, tumor specific mutations.\(^3\),\(^4\)
- Some tumor specific mutations can be recognized by the immune system (neo-antigen).\(^5\)
- These neo-antigens can mediate tumor rejection.\(^6\),\(^7\)

2. Srivastava and Old Immunology Today 1988
5. Many examples see http://cancerimmunity.org/peptide/mutations/
6. Dubey et al. JEM. 1997
7. Ikeda et al. PNAS. 1997
8. Matsutake et al. PNAS. 2001

Srivastava et al. Immunity 1998
Srivastava and Old. Immunology Today 1988
Lessons learned from mice (and applied to men)

In Men ...

- Human tumors harbor 100's – 1000's of mutations and 10'-100's of these are predicted to represent neo-antigens.¹,²
- Immune responses in cancer patients include T cells specific for some mutated proteins.³
- Responses to neo-antigens may be associated with activity of ipilimumab.⁴
- T cells specific for a neo-antigen can mediate tumor rejection.⁵


Tran et al. Science 2014

Presented by: Margaret Callahan

Presented By Margaret Callahan at 2014 ASCO Annual Meeting
Are BRCA1/2 tumors more immunogenic due to higher levels of mutations?

- BRCA1 and BRCA2 mutation-associated tumors contain high levels of genome instability due to defects in normal DNA repair
  - With increasing mutational burden, there is increased potential that the immune system will recognize a neoantigen in the tumor

- Could this increased burden of neoantigens render BRCA1/2 tumors more amenable to immunotherapies?
  - No answers yet, but very hot topic
  - Stay tuned
• Programmed death 1 (PD-1) is expressed on T cells
  • Inhibits killing by T cells when binds to PD-L1
  • PD-L1 expressed on tumors or in the tumor microenvironment

• Many antibody drugs now targeting PD-1 and PD-L1
  • Impressive activity in melanoma, kidney cancer, lung cancer, others

PD-L1 and BRCA1

- Recently reported study showed that 7/7 BRCA1 mutant tumors also expressed PD-L1
  - ~20% positive in unselected TNBC

- Elevated PD-L1 expression in TNBC was significantly associated with DNA repair genes
  - Low expression of BRCA1
  - Low expression of FANCA

Summary

- Growing evidence that platinum-based therapy is active in both advanced & early-stage TNBC
  - Not yet practice changing in early breast cancer
  - Randomized data urgently needed in mTNBC

- Efficacy influenced by BRCA1/2 mutation status
  - BRCA1/2 mutation carriers achieve higher response rates
  - This information needs to be more routinely captured in trials

- Beyond BRCA1 and BRCA2, other germline biomarkers associated with therapeutic sensitivity likely exist
  - Studies needed in this space
Summary

- Certain sporadic TNBC patients likely stand to benefit significantly from a platinum-based approach.

- Ultimately, measures of global genomic instability (e.g. HRD) may have the greatest potential to identify those patients who stand to benefit most from a DNA repair defect-targeted approach.

- Immunotherapy approaches may prove relevant for TN & BRCA1/2+ breast cancer.
  - Urgently need clinical trials in this space.

Careful randomized clinical trial designs that incorporate biomarkers of response are key.
Thank you!