Triple-negative breast cancer: A medical update just for you

Melinda Telli, M.D.

Stanford University School of Medicine

September 24, 2016
Outline

- Clinical features of TNBC
- Medical update on therapeutics in early stage TNBC
  - Platinums
  - PARP inhibitors
  - Capecitabine after neoadjuvant chemotherapy
- Current & upcoming studies in early stage TNBC

*Will leave plenty of time for discussion, Q & A*
Important subsets of breast cancers defined by molecular markers

Take away:

• Breast cancer is not one disease
The breast cancer markers ER, PR and HER2 are **prognostic** (various combinations may be favorable or unfavorable); they also are **predictive** (tell us which types of therapies are likely to be of benefit or not).
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)

Triple-Negative Breast Cancer

Current Status

- Standard treatment for early-stage TNBC in 2016 consists of combination chemotherapy
  - Anthracycline and taxane-based
  - Has not changed significantly in 15+ years

- No targeted therapies yet approved
TNBC patients with no residual cancer after standard neoadjuvant chemotherapy have excellent prognosis

Neoadjuvant treatment allows opportunities for post-neoadjuvant studies with novel agents in patients with residual disease

Recurrence when it happens is early

Sites of First Distant Recurrence

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 & inherited mutations in BRCA1/2

- Approximately 75-80% of BRCA1 mutation-associated breast cancers are triple-negative\(^1,2\)

- In unselected TNBC, frequency of BRCA1/2 mutations reported to be up 11 - 19.5% \(^3-5\)

4. Sharma BCRT, 2015
Breast Cancer Genes: The Landscape

- Many other genes implicated in familial breast cancer
  - Many in DNA repair pathways
- Among 1800 patients with TNBC, in addition to BRCA1 and BRCA2, ~4% of patients had mutations in these genes:
  - PALB2, BARD1, BRIP1, Rad51c, Rad51D, Rad50
- DNA repair-targeted therapy is hypothesized to have a role in these patients

Figure 2. Breast-Cancer Susceptibility Loci and Genes.

**Platinum**

- Cisplatin first approved by the FDA in 1978
  - Noted to have activity in metastatic breast cancer\(^1\)

- 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

---

Neoadjuvant 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 TNBC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Regimen</th>
<th>pCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba GEICAM 2006-03</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, 30% no Cp</td>
</tr>
<tr>
<td>von Minckwitz GeparSixto</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, 37% no Cp</td>
</tr>
<tr>
<td>Sikov CALGB 40603</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, 41% no Cp, 52% with Bev, 44% no Bev</td>
</tr>
</tbody>
</table>
TNBC:

- Bevacizumab 15 mg/kg q3w

GeparSixto Therapy in TNBC subgroup

N=315 centrally confirmed TNBC

R

PM

PMCb

Paclitaxel 80 mg/m² q1w

Non-pegylated liposomal doxorubicin 20 mg/m² q1w

Carboplatin AUC 1.5-2* q1w

Surgery

TNBC: Bevacizumab 15 mg/kg q3w

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

OR 1.94 (1.24 – 3.04)
P = 0.005

von Minckwitz et al. Lancet Oncology, May 2014
Disease-free Survival: Effect of Carboplatin in TNBC

Logrank $p=0.0325$
HR PMCb to PM = 0.56, 95% CI (0.33, 0.96), $p=0.0350$

von Minckwitz et al. SABCS 2015

Median DFS Follow-up = 35 months
Paclitaxel 80 mg/m² wkly x 12  
**ddAC x 4**

Paclitaxel 80 mg/m² wkly x 12  
**ddAC x 4**
Bevacizumab 10 mg/kg q2wks x 9

Paclitaxel 80 mg/m² wkly x 12  
**ddAC x 4**
Carboplatin AUC 6 q3wks x 4

Paclitaxel 80 mg/m² wkly x 12  
**ddAC x 4**
Carboplatin AUC 6 q3wks x 4
Bevacizumab 10 mg/kg q2wks x 9

2 x 2 Randomization

CALGB 40603: pCR Breast/Axilla

+/- Carboplatin

| 41% (35-48%) | 54% (48-61%) |

Odds ratio: 1.71
p = 0.0029

N=212  N=221

CALGB 40603 – Event–free survival for carboplatin vs. not

HR = 0.84 (0.58-1.22), p = 0.36

No Cb 3-yr = 71%
Cb 3-yr = 76%

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Years from Study Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>No Cb</td>
<td>218</td>
</tr>
<tr>
<td>Cb</td>
<td>225</td>
</tr>
</tbody>
</table>

This presentation is the intellectual property of the authors. Contact them at wsikov@wihri.org for permission to reprint and/or distribute.
Neoadjuvant TNBC platinum data in context

- At this time, the routine addition of platinum to standard anthracycline and taxane-based therapy is not recommended
  - Inconsistent results regarding longer term outcomes in GeparSixto and CALGB 40603
  - Both GeparSixto and CALGB 40603 studies were underpowered for long-term survival endpoints and both incorporated bevacizumab

- Ultimate survival benefits need to be assessed in definitive phase III carboplatin TNBC trials
- NRG BR003 now enrolling patients
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)
PARP inhibitors in advanced BRCA positive 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
I-SPY 2: Carboplatin + Veliparib
Arm in TNBC

Taxol – AC pCR = 26%
Taxol/Carbo/Veliparib – AC pCR = 51%

Phase 3 Brightness trial testing this combination just concluded enrollment

Rugo H et al. NEJM 2016
Can standard capecitabine chemotherapy improve outcomes in patients with residual cancer after neoadjuvant treatment?

**CREATE-X: Trial Design**

- **HER2-**
  - NAC
  - Surgery
  - Pathology Non-pCR or node +
  - (n=900)

- **Control:** Standard therapy
- **Standard therapy + Capecitabine**

**Stratification factors:**
- ER, Age, NAC, ypN, 5FU and institution

**Standard therapy:**
- HR+: Hormone therapy
- HR-: No further systemic treatment
Among patients with residual cancer after standard preoperative chemotherapy:

- 6 months of oral capecitabine (Xeloda) decreased recurrences & improved survival
- Biggest effect in TNBC subgroup
Ongoing & Upcoming Clinical Trials of Interest for Early Stage TNBC
**EA1131: Post-neoadjuvant study of platinum versus capecitabine**

**ONGOING**

Patients with:
- stage II/III TNBC
- Neoadjuvant chemotherapy
- found to have $\leq 1$ cm in diameter of residual cancer in the breast at the time of definitive surgery

**Stratification factors:**
1. Clinical stage at diagnosis (II or III)
2. Residual cancer burden after NAC (1～3 cm or $>3$ cm)
3. Planned platinum agent choice (cisplatin or carboplatin)
4. Anthracycline exposure (yes or no)
5. Administration of radiotherapy (yes or no)
6. Basal-like subtype (yes no)

**Accrual = 750**
1 cycle = 3 weeks

**Arm A**
- Observation

**Arm B**
- Cisplatin 75 mg/m² Day 1 every Q3W x 4 cycles OR Carboplatin AUC 6 Day 1 Q3W x 4 cycles

**Arm C**
- Capecitabine 1000 mg/m² twice daily D1-14 every Q3wx6 cycles

**Step 0**
- Screening

**Step 1**
- Randomize
- Tissue Submission
- PAM50 analysis

CLOSED TO NEW ACCRUAL**

**Notes:**
1. TNBC: ER/PR less than 10% positive staining with weak intensity score, or less than 1% positive staining with weak or intermediate intensity score; HER2 negative per ASCO guidelines.
2. Taxane ± anthracycline based; platinum agents or capecitabine not allowed.
3. Choice of platinum agent will be per treating physician discretion.
4. Primary Endpoint: IDFS in patients with basal-like TNBC.
5. Secondary Endpoints: IDFS in patient with non basal-like TNBC, OS and RFS.
6. Patients must have completed adjuvant radiotherapy (if applicable) prior to randomization.
7. Tumor tissue from the residual disease on the definitive surgical specimen must be submitted within 21 weeks post surgery for PAM50 analysis for stratification as outlined in Section 10.2. Patients cannot be randomized to treatment until confirmation of PAM50 analysis from the Molecular Diagnostics Laboratory performing the assessments.
8. Females of child-bearing potential must have a blood test or urine study within 2 weeks prior to treatment initiation to rule out pregnancy.

**Rev. 5/16**
- Arm A closed to new accrual in Addendum #3. New patients are randomized to Arm B or C.

---

**Accrual = 750**
1 cycle = 3 weeks

**Notes:**
1. TNBC: ER/PR less than 10% positive staining with weak intensity score, or less than 1% positive staining with weak or intermediate intensity score; HER2 negative per ASCO guidelines.
2. Taxane ± anthracycline based; platinum agents or capecitabine not allowed.
3. Choice of platinum agent will be per treating physician discretion.
4. Primary Endpoint: IDFS in patients with basal-like TNBC.
5. Secondary Endpoints: IDFS in patient with non basal-like TNBC, OS and RFS.
6. Patients must have completed adjuvant radiotherapy (if applicable) prior to randomization.
7. Tumor tissue from the residual disease on the definitive surgical specimen must be submitted within 21 weeks post surgery for PAM50 analysis for stratification as outlined in Section 10.2. Patients cannot be randomized to treatment until confirmation of PAM50 analysis from the Molecular Diagnostics Laboratory performing the assessments.
8. Females of child-bearing potential must have a blood test or urine study within 2 weeks prior to treatment initiation to rule out pregnancy.

**Rev. 5/16**
- Arm A closed to new accrual in Addendum #3. New patients are randomized to Arm B or C.
SWOG/NRG S1418: Post-neoadjuvant immunotherapy study

A Randomized, Phase III Trial to Evaluate the Efficacy and Safety of Pembrolizumab (MK-3475) as Adjuvant Therapy for TNBC with > 1 cm Residual Invasive Cancer or Positive Lymph Nodes (pN1) After Neoadjuvant Chemotherapy

**SOON TO ACTIVATE**

- TNBC
- > 1 cm residual cancer or any + LN after neoadjuvant chemotherapy

Randomize 1:1
Stratified by:
- N+ vs N1
- T1 vs T≥2
- PDL1 + vs –
- Adjuvant chemo yes vs no

MK3475
200mg IV q3wk x 1 year

Observation

5 yr Follow-up

Additional large studies of standard chemotherapy + immunotherapy being planned at this time
Adjuvant PARP inhibitor study in BRCA+
ONGOING

OlympiA
Design and Eligibility

- HER2 negative with BRCA 1 or 2 mutation
Post adjuvant chemotherapy
  • TNBC
    • Node positive disease (any tumour size) OR
    • Node negative, primary > 2 cm
  • ER+ ≥ 4 positive nodes

- HER2 negative with BRCA 1 or 2 mutation
- Post NAC with residual disease
  • TNBC - any residual invasive disease in breast or nodes
  • ER+ - CPS+EG score ≥ 3

Randomize 1:1
Double blind
N=1500

Olaparib
300 mg bid
12 month duration

Placebo
12 month duration

IDFS
Distant DFS; OS
Summary

- Growing evidence that therapies targeting DNA repair defects are active in TNBC
  - Results of large phase 3 studies testing platinums and PARP inhibitors are eagerly awaited

- Efficacy influenced by BRCA1/2 mutation status
  - BRCA1/2 mutation carriers achieve higher response rates

- Beyond BRCA1 and BRCA2, other inherited gene mutations have been recently associated with TNBC

- Capecitabine recently shown to improve survival in a phase 3 trial in patients with residual cancer after standard neoadjuvant therapy

- Multiple studies underway to assess additional therapies following standard chemotherapy in TNBC
  - Platinums, PARP inhibitors, immunotherapy
Thank you!