Chemotherapy in Triple-negative Breast Cancer: is it better to use platinum agents and why?

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Molecular subtypes of breast cancer

- **Luminal A**: ER+ and/or PR+, HER2-; low grade
- **Luminal B**: ER+ and/or PR+, HER2+, Ki 67 high; high grade
- **Basal-like/triple negative**: ER-, PR- and HER2-
  - Most BRCA1 breast cancers are basal-like TNBC
  - Most triple negative tumors are basal-like and most basal-like tumors are triple negative. However, not all triple negative tumors are basal-like and not all basal-like tumors are triple negative
- **ERBB2/HER2+**: has amplified HER2/neu; ER and PR -
- Normal breast-like
- **Claudin-low**: a more recently described class; often triple-negative, but distinct in that there is low expression of cell-cell junction proteins including E-cadherin and frequently there is infiltration with lymphocytes
Triple-negative breast cancer

- Triple-negative breast cancer, characterized by tumors that do not express estrogen receptor (ER), progesterone receptor (PR), or HER-2 genes.
- 10%-20% of all BC are triple-negative breast cancer.
- Women with triple-negative breast cancer are at greater risk of relapse for every stage of breast cancer.
## Characteristics of Basal/TN Breast Cancers

| Epidemiological features | Younger age  
|                          | Pre-menopausal status  
|                          | African-American race  
|                          | High BMI  
|                          | Younger age at menarche  
| Histoclinical features   | Ductal carcinoma (and medullary)  
|                          | High-grade  
|                          | High mitotic index  
|                          | Nuclear pleomorphism  
|                          | Pushing margins of invasion  
|                          | Central necrosis  
|                          | Negative ER, PR and ERBB2 IHC staining  
|                          | Poor correlation between pathological tumor size and axillary lymph node status  
| Molecular features       | TP53 mutations  
|                          | BRCA1-deficiency  
|                          | RB inactivation  
|                          | Genome instability (« complex pattern »)  
| Prognosis                | Poor prognosis  
|                          | Early relapses (first 3 years)  
|                          | Visceral metastases (brain, lung)  
| Therapeutic response     | Sensitive to primary chemotherapy  
|                          | No validated targeted therapy (ongoing trials)  

Triple-negative breast cancer—histology

Basal-like and Triple-Negative Breast Cancers

Low-grade tumors

- Secretory carcinoma
- Adenoid cystic carcinoma

High-grade tumors

- Medullary breast cancer
- Metaplastic breast cancer
- Grade 3 – IDC-NST
Triple-negative breast cancer: Recurrence and survival

*Kim K, Lee E, Lee J; Korea Breast Cancer Society. Clinicopathologic Signature of TNBC Patients with Good Prognosis. SABCS December 15, 2009; San Antonio, Texas
Triple-Negative Breast Cancer: Hazard Rates for Distant Recurrence

Median time to distant recurrence
TNBC = 2.6 years
Other breast cancer = 5 years
\( P < 0.0001 \)

Prevalence of BRCA1 Mutation in Patients With TNBC

- There are phenotypic and molecular similarities between BRCA1-associated breast cancer and sporadic triple-negative breast cancer, and 10% to 20% of triple-negative breast cancers harbor germline BRCA mutations.

Table 1  Studies with over 50 cases that have evaluated BRCA1 mutation prevalence in TN cancers

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>BRCA1 mutations (%)</th>
<th>Unselected/selected</th>
<th>Selection criteria</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>144</td>
<td>20 (14)</td>
<td>Unselected</td>
<td>Bilateral and/or family history of breast cancer.</td>
<td>Collins et al (2009)</td>
</tr>
<tr>
<td>96</td>
<td>9 (9)</td>
<td>Selected</td>
<td>Bilateral and/or family history of breast cancer.</td>
<td>Zhang et al (2011)</td>
</tr>
<tr>
<td>93</td>
<td>32 (34)</td>
<td>Selected</td>
<td>Seen in Genetic clinics and underwent BRCA testing.</td>
<td>Atchley et al (2008)</td>
</tr>
<tr>
<td>77</td>
<td>12 (16)</td>
<td>Unselected</td>
<td>Bilateral and/or family history of breast cancer.</td>
<td>Gonzalez-Angulo et al (2011)</td>
</tr>
<tr>
<td>63</td>
<td>8 (13)</td>
<td>Selected and unselected</td>
<td>TN &lt; 41 years</td>
<td>Evans et al (2011)</td>
</tr>
<tr>
<td>54</td>
<td>5 (9)</td>
<td>Selected</td>
<td>TN &lt; 40 years and did not qualify for testing according to ASCO guidelines</td>
<td>Young et al (2009)</td>
</tr>
</tbody>
</table>

Abbreviation: TN = Triple-negative.

Systemic treatment recommendations for early breast cancer subtypes /ESMO/  

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Recommended therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A-like</td>
<td>ET alone in the majority of cases.</td>
<td>Consider CT if high tumour burden (four or more positive LN, T3 or higher) grade 3</td>
</tr>
<tr>
<td>Luminal B-like (HER2-negative)</td>
<td>ET + CT for the majority of cases</td>
<td></td>
</tr>
<tr>
<td>Luminal B-like (HER2-positive)</td>
<td>CT + anti-HER2 + ET for all patients</td>
<td>If contraindications for the use of CT, one may consider ET + anti-HER2 therapy, although no randomised data exist</td>
</tr>
<tr>
<td>HER2-positive (non-luminal)</td>
<td>CT + anti-HER2</td>
<td></td>
</tr>
<tr>
<td>Triple-negative (ductal)</td>
<td>CT</td>
<td></td>
</tr>
</tbody>
</table>
Chemotherapy in TNBC

- Triple negative/basal-like tumors are usually treated with some combination of surgery, radiation therapy and chemotherapy.
- These tumors cannot be treated with hormone therapies or trastuzumab (Herceptin) because they are ER- and HER2-.
- Current treatment strategies for triple-negative breast cancer include:
  - anthracyclines,
  - taxanes,
  - ixabepilone,
  - platinum agents,
  - selected biologic agents,
  - possibly anti-EGFR drugs.
Anthracyclines for triple-negative breast cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase/no. TNBC pts</th>
<th>Setting</th>
<th>Regimen</th>
<th>Outcome in TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Leo (2008) meta-analysis</td>
<td>III (n = 157)</td>
<td>Adjuvant</td>
<td>Anthracycline regimens vs CMF</td>
<td>23% reduction in risk of relapse (p=0.11)</td>
</tr>
<tr>
<td>Bidard (2008)</td>
<td>II (n = 120)</td>
<td>Neoadjuvant</td>
<td>CEF x 4–6</td>
<td>Pathological complete response = 17%</td>
</tr>
<tr>
<td>Gluz (2008)</td>
<td>III (n = 66)</td>
<td>Neoadjuvant</td>
<td>DD EC or CMF vs HD EC-ECthiotepa</td>
<td>5-yr event-free survival with HD 71% vs 26% with DD</td>
</tr>
</tbody>
</table>

- C-cyclophosphamide; DD- dose dense; E- epirubicin; F- 5-fluorouracil; HD- high dose; M- methotrexate, TNBC triple negative breast cancer.
Platinum agents for triple-negative breast cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase/no. of TNBC pts</th>
<th>Setting</th>
<th>Regimen</th>
<th>Outcome in TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sikov (2009)</td>
<td>II (n = 12)</td>
<td>Neoadjuvant</td>
<td>Carbo-P vs Carbo-P-trastuzumab</td>
<td>pCR = 67%</td>
</tr>
<tr>
<td>Torrisi (2008)</td>
<td>II (n = 30)</td>
<td>Neoadjuvant TNBC</td>
<td>Epirubicin-Cis-5-fluorouracil»P</td>
<td>pCR = 40%; ORR = 86%</td>
</tr>
<tr>
<td>Silver (2010)</td>
<td>II (n = 28)</td>
<td>Neoadjuvant TNBC</td>
<td>Cis</td>
<td>pCR = 22%</td>
</tr>
<tr>
<td>Leone (2009)</td>
<td>Retrospective (n = 125)</td>
<td>Neoadjuvant TNBC</td>
<td>Platinum + docetaxel</td>
<td>pCR = 34%</td>
</tr>
<tr>
<td>Uhm (2009)</td>
<td>II (n = 36)</td>
<td>Metastatic</td>
<td>Carbo-P or Cis-P</td>
<td>ORR = 37.5%</td>
</tr>
</tbody>
</table>

- Carbo- carboplatin; Cis-cisplatin; ORR- overall response rate; P-paclitaxel; pCR-pathological complete response; TNBC triple-negative breast cancer
## Ixabepilone for triple-negative breast cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Setting</th>
<th>Regimen</th>
<th>Outcome in TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivot (2009)</td>
<td>III (n = 187)</td>
<td>Metastatic breast cancer resistant to anthracycline or taxane</td>
<td>Ixabepilone + cape vs cape alone</td>
<td>Improved overall response rate (27% vs 9%) and progression-free survival 4.1 vs 2.1 mo(s)</td>
</tr>
<tr>
<td>Baselga (2009)</td>
<td>II (n = 161)</td>
<td>Neoadjuvant</td>
<td>Ixabepilone</td>
<td>Pathological complete response = 26%</td>
</tr>
</tbody>
</table>

- TNBC-triple negative breast cancer; cape-capecitabine.
Anthracyclin and taxane pretreated TNBC patients.

GSF: Granulocyte stimulating factor; ORR: Overall response rate; PFS: Progression free survival; DFS: Disease free survival; DDFS: Distant disease free survival; TNBC: Triple-negative breast cancer; P: Paclitaxel; FEC: 5-Fluorouracil, epirubicin, cyclophosphamide.

*Yadav BS et al. Treatment of triple-negative breast cancer; World J Clin Oncol 2014 May
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Yr</th>
<th>No.</th>
<th>Regimen</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garber <em>et al</em>[^20]</td>
<td>2006</td>
<td>28</td>
<td>Cisplatin</td>
<td>21%</td>
</tr>
<tr>
<td>Silver <em>et al</em>[^21]</td>
<td>2010</td>
<td>28</td>
<td>Cisplatin 3 wk × 4</td>
<td>22%</td>
</tr>
<tr>
<td>Byrski <em>et al</em>[^22]</td>
<td></td>
<td>12</td>
<td>Cisplatin</td>
<td>83%</td>
</tr>
<tr>
<td>Byrski <em>et al</em>[^23]</td>
<td>2009</td>
<td>25</td>
<td>Cisplatin + paclitaxel + GSF</td>
<td>72%</td>
</tr>
<tr>
<td>Ryan <em>et al</em>[^24]</td>
<td>2009</td>
<td>51</td>
<td>Cisplatin + bevacizumab 3 wk × 4</td>
<td>72%</td>
</tr>
<tr>
<td>Frasci <em>et al</em>[^25]</td>
<td>2009</td>
<td>74</td>
<td>Cisplatin + epirubicin + paclitaxel wk × 8</td>
<td>65%</td>
</tr>
<tr>
<td>Sikov <em>et al</em>[^27]</td>
<td>2007</td>
<td>10</td>
<td>Carboplatin 3 wk × 4 + paclitaxel wk × 16</td>
<td>50%</td>
</tr>
<tr>
<td>Leone <em>et al</em>[^28]</td>
<td>2009</td>
<td>125</td>
<td>Platinum[^1] + docetaxel 3 wk × 4</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Platinum + docetaxel → AC 3 wk × 4</td>
<td>40%</td>
</tr>
</tbody>
</table>

[^1]: Cisplatin or carboplatin; BRCA1 mutation carriers. AC: Doxorubicin + cyclophosphamide; 5-FU: 5-Fluorouracil; PCR: Pathological complete response; cCR: Clinical complete response; GSF: Granulocyte stimulating factor.
**Table 4 Clinical outcomes with targeted therapy in metastatic triple-negative breast cancer**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Line of treatment</th>
<th>Regimen</th>
<th>No.</th>
<th>ORR (%)</th>
<th>CBR (%)</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Shaughnessy et al.</td>
<td>First line</td>
<td>Gemcitabine + Carboplatin ± Inipar²</td>
<td>61</td>
<td>52</td>
<td>56</td>
<td>5.9</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>62</td>
<td>32</td>
<td>34</td>
<td>3.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Isakoff et al.</td>
<td>First line</td>
<td>Velipar² + TMZO</td>
<td>41</td>
<td>37.5</td>
<td>62.5</td>
<td>5.5</td>
<td>NR</td>
</tr>
<tr>
<td>Carey et al.</td>
<td>First line</td>
<td>Cetuxim³</td>
<td>71</td>
<td>18</td>
<td>31</td>
<td>2²</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin¹</td>
<td>54</td>
<td>6</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O'Shaughnessy et al.</td>
<td>First or second line</td>
<td>Irinotecan + Carboplatin ± Cetuxim²</td>
<td>52</td>
<td>49</td>
<td>NR</td>
<td>5.1</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51</td>
<td>30</td>
<td></td>
<td>4.7</td>
<td>12.3</td>
</tr>
<tr>
<td>Finn et al.</td>
<td>First line</td>
<td>Dasatinib²</td>
<td>44</td>
<td>4.6</td>
<td>9.2</td>
<td>8.3 wk</td>
<td>NR</td>
</tr>
<tr>
<td>Baselga et al.</td>
<td>First or second line</td>
<td>Cisplatin ± Cetuxim²</td>
<td>115</td>
<td>20</td>
<td>NR</td>
<td>3.7³</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>58</td>
<td>10</td>
<td></td>
<td>1.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Gray et al.</td>
<td>First line</td>
<td>Paclitaxel ± Bevacizum³</td>
<td>122</td>
<td>48</td>
<td>NR</td>
<td>11.8³</td>
<td>NR</td>
</tr>
<tr>
<td>(E2100)</td>
<td></td>
<td></td>
<td>111</td>
<td>22</td>
<td></td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Miles et al.</td>
<td>First line</td>
<td>Docetaxel ± Bevacizum³</td>
<td>58</td>
<td>64</td>
<td>NR</td>
<td>10³</td>
<td>NR</td>
</tr>
<tr>
<td>(AVADO)</td>
<td></td>
<td></td>
<td>53</td>
<td>46</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Robert et al.</td>
<td>First line</td>
<td>Tax/Anthr¹ ± Bevacizum³</td>
<td>96</td>
<td>NR</td>
<td>NR</td>
<td>6.5</td>
<td>NR</td>
</tr>
<tr>
<td>(RiBBON-1)</td>
<td></td>
<td></td>
<td>46</td>
<td></td>
<td></td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Brufsky et al.</td>
<td>Second line</td>
<td>Cap, tax, gem/vinorel, ± Bevacizum³</td>
<td>112</td>
<td>41³</td>
<td>NR</td>
<td>6.0³</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47</td>
<td>18</td>
<td></td>
<td>2.7</td>
<td>12.6</td>
</tr>
</tbody>
</table>

¹Cross over to cetuximab + carboplatin arm after progressive disease; ²For entire cohort; ³Significant. TMZO: Temozolamide; ORR: Overall response rate; CBR: Clinical benefit rate; PFS: Progression free survival; NR: Not reported; Tax: Taxanes; Cap: Capecitabine; Gem: gemcitabine

*Yadav BS et al. Treatment of triple-negative breast cancer; World J Clin Oncol 2014 May
Chemotherapy in TNBC

• Platinum has received much attention recently for the treatment of newly diagnosed triple-negative breast cancer (TNBC).

• Silver et al (Efficacy of Neoadjuvant Cisplatin in Triple Negative BC) demonstrated that pCR after cisplatin was significantly higher in TNBC with low BRCA1 mRNA expression.

• Randomised phase II studies are showing improvement in pathologic complete response in early-stage TNBC when carboplatin is added to the anthracycline/taxane treatment backbone (ASCO 2014)

• Two randomized phase II neoadjuvant trials, GeparSixto and CALGB (Cancer and Leukemia Group B) 40603 (Alliance), reported that pathologic complete response (pCR) rates were approximately 15% higher with the addition of carboplatin to anthracyclines and taxanes.
Randomised phase II study of weekly paclitaxel with or without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA HER-2 negative breast cancer (Tamura et al.)

- Women who received carboplatin had a significantly improved pathologic complete response compared to those who received paclitaxel alone before CEF.

<table>
<thead>
<tr>
<th>CT</th>
<th>Nº pt</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>paclitaxel with carboplatin</td>
<td>88</td>
<td>31.8%</td>
</tr>
<tr>
<td>paclitaxel without carboplatin</td>
<td>91</td>
<td>17.6%</td>
</tr>
</tbody>
</table>

(p=0.01)
Results in the triple-negative subgroup

- Among the 181 eligible patients, there were 75 with triple-negative breast cancer.

<table>
<thead>
<tr>
<th>CT</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>with carboplatin</td>
<td>61.2%</td>
</tr>
<tr>
<td>without carboplatin</td>
<td>26.3%</td>
</tr>
</tbody>
</table>

(p=0.003)
## Results - Toxicity

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>neutropenia gr 3 – 4</strong></td>
<td></td>
</tr>
<tr>
<td>with carboplatin</td>
<td>65.9%</td>
</tr>
<tr>
<td>without carboplatin</td>
<td>38.5%</td>
</tr>
</tbody>
</table>
Results - EGFR expression

- EGFR, CK 5/6 and BRCA 1 expressions were significantly frequent in TNBC (46 tumor samples; 21%)

<table>
<thead>
<tr>
<th></th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR positive</td>
<td>45%</td>
</tr>
<tr>
<td>EGFR negative</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

(p=0.010)

- Among those receiving carboplatin with paclitaxel

<table>
<thead>
<tr>
<th></th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR positive</td>
<td>63.8%</td>
</tr>
<tr>
<td>EGFR negative</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

(p=0.040)
Conclusions

- Adding CBDCA to neoadjuvant wPTX followed by CEF for HNBC statistically significantly improved pCR rate with a favorable safety profile.

- EGFR expression by IHC is a potent predictive biomarker of response to the CP-CEF regimen as NAC.
GeparSixto: Neoadjuvant Carboplatin Chemotherapy in TNBC Subgroup

Centrally confirmed TNBC with clinical stage T2-T4a-d or T1c with N+ disease (N = 315)[1]
Subgroup of main study with HER2+ or TNBC (N = 595)[2]

- Primary endpoint of subanalysis: compare pCR (ypTo ypNo) with or without carboplatin
- Secondary endpoint of subanalysis: correlate germline BCRA alterations and/or family history for breast or ovarian cancer with pCR

# GeparSixto: Baseline Characteristics of Patients in the TNBC Subgroup

<table>
<thead>
<tr>
<th></th>
<th>PM (N = 146)</th>
<th>PMCb (N = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (yrs)</td>
<td>47</td>
<td>47.5</td>
</tr>
<tr>
<td>Median tumor size, cm</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>cT3-T4, %</td>
<td>13.7</td>
<td>8.1</td>
</tr>
<tr>
<td>cN+, %</td>
<td>45.1</td>
<td>40.6</td>
</tr>
<tr>
<td>Grade 3, %</td>
<td>77.4</td>
<td>72.3</td>
</tr>
<tr>
<td>Family history for BC/OC,* %</td>
<td>34.9</td>
<td>33.8</td>
</tr>
<tr>
<td>Any genetic alteration, %</td>
<td>15.8</td>
<td>14.2</td>
</tr>
<tr>
<td>gBRCA 1</td>
<td>13</td>
<td>10.8</td>
</tr>
<tr>
<td>gBRCA 2</td>
<td>1.4</td>
<td>2.7</td>
</tr>
<tr>
<td>gRAD50/51C</td>
<td>1.4</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Assessed using German BRCA consortium checklist to identify pts at risk for germline alterations >10%.

GeparSixto: pCR in Patients With TNBC

<table>
<thead>
<tr>
<th>Family History for BC/OC</th>
<th>gBRCA/RAD Alteration</th>
<th>ypT0 ypN0</th>
<th>ypT0/is ypN0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 250)</td>
<td>Yes (n = 44)</td>
<td></td>
</tr>
<tr>
<td>No (n = 193)</td>
<td>40.4% (69/171)</td>
<td>45.5% (10/22)</td>
<td></td>
</tr>
<tr>
<td>Yes (n = 101)</td>
<td>44.3% (35/79)</td>
<td>63.6% (14/22)</td>
<td></td>
</tr>
</tbody>
</table>

**GeparSixto: Prediction of Carboplatin Effect on pCR in Patients With TNBC**

<table>
<thead>
<tr>
<th>pCR, %</th>
<th>PM (n = 146)</th>
<th>PMCb (n = 149)</th>
<th>Δ, PM vs PMCb</th>
<th>OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factor</td>
<td>34.5</td>
<td>46</td>
<td>11.5</td>
<td>1.61</td>
<td>.13</td>
</tr>
<tr>
<td>Family history of BC/OC without alteration</td>
<td>30.8</td>
<td>57.5</td>
<td>26.7</td>
<td>3.04</td>
<td>.02</td>
</tr>
<tr>
<td>gBRCA/RAD alteration with/without family history</td>
<td>43.5</td>
<td>66.7</td>
<td>23.2</td>
<td>2.6</td>
<td>.13</td>
</tr>
</tbody>
</table>

GeparSixto: Summary

- Alterations of gBRCA or gRAD50/51 detectable in ≥ 15% of participants with TNBC from GeparSixto trial
- pCR rates higher in patients with family history of BC/OC (49%), gBRCA/RAD alterations (55%), or both risk factors (64%) compared with neither risk factor (40%)
- Increase in pCR rate with carboplatin highest in patients with family history (26%) and gBRCA/RAD alterations (23%)
- Germline mutation status and family history may help identify patients who can benefit from adding carboplatin to neoadjuvant chemotherapy
- Questions remain on use of platinum agents in standard neoadjuvant therapy (dose-dense AC followed by paclitaxel)

Impact of the addition of Carboplatin and/or Bevacizumab to neoadjuvant once-per-week Paclitaxel followed by dose-dense Doxorubicin and Cyclophosphamide on pathologic complete response rates in Stage II to III triple-negative breast cancer: CALGB 40603 (Alliance)

- CALGB 40603 (Alliance), a 2 x 2 factorial, open-label, randomized phase II trial, evaluated the impact of adding carboplatin and/or bevacizumab.
CALGB 40603 (Alliance) - patients and methods

Arm 1
- Paclitaxel 80 mg/m² once per week × 12
- ddAC × 4

Arm 2
- Paclitaxel 80 mg/m² once per week × 12
- Bevacizumab 10 mg/kg once every 2 weeks × 9
- ddAC × 4

Arm 3
- Paclitaxel 80 mg/m² once per week × 12
- Carboplatin AUC 6 once every 3 weeks × 4
- ddAC × 4

Arm 4
- Paclitaxel 80 mg/m² once per week × 12
- Carboplatin AUC 6 once every 3 weeks × 4
- Bevacizumab 10 mg/kg once every 2 weeks × 9
- ddAC × 4

Research biopsies frozen and fixed

Surgery*†
XRT†
No adjuvant systemic treatment planned†
## Patient demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total patients (N=443)</th>
<th>Arm One: wP→ddAC (n=108; %)</th>
<th>Arm Two: wP→ddAC + Bev (n=110; %)</th>
<th>Arm Three: wPCarbo→ddAC (n=113; %)</th>
<th>Arm Four: wPCarbo→ddAC + Bev (n=112; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>103</td>
<td>21</td>
<td>28</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>40-59</td>
<td>266</td>
<td>59</td>
<td>57</td>
<td>57</td>
<td>67</td>
</tr>
<tr>
<td>≥60</td>
<td>74</td>
<td>19</td>
<td>15</td>
<td>23</td>
<td>10</td>
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<tr>
<td><strong>Race</strong></td>
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<td></td>
<td></td>
<td></td>
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<td>White</td>
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<td>74</td>
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<td>19</td>
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<td>Other/missing</td>
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<td><strong>Clinical stage</strong></td>
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<td></td>
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<tr>
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<td>67</td>
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<tr>
<td>III</td>
<td>143</td>
<td>31</td>
<td>34</td>
<td>32</td>
<td>33</td>
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<tr>
<td><strong>Tumor grade</strong></td>
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</tr>
<tr>
<td>Low</td>
<td>6</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>Intermediate</td>
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<tr>
<td>High</td>
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<tr>
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<td>8</td>
<td>14</td>
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</table>
### Patient demographic and clinical characteristics—cont.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total patients (N=443)</th>
<th>Arm One: wP→ddAC (n=108; %)</th>
<th>Arm Two: wP→ddAC + Bev (n=110; %)</th>
<th>Arm Three: wPCarbo→ddAC (n=113; %)</th>
<th>Arm Four: wPCarbo→ddAC + Bev (n=112; %)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td><strong>T stage</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>4</td>
</tr>
<tr>
<td>Missing</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td><strong>N stage</strong></td>
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<td></td>
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<tr>
<td>0</td>
<td>186</td>
<td>42</td>
<td>45</td>
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<tr>
<td>1</td>
<td>184</td>
<td>42</td>
<td>42</td>
<td>47</td>
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</tr>
<tr>
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<td>30</td>
<td>7</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

Bev-bevacizumab; Carbo-carboplatin; ddAC dose-dense doxorubicin plus cyclophosphamide; wP–paclitaxel once per week.
Delivery of wP and ddAC by treatment arm

- Patients assigned to either carboplatin or bevacizumab were less likely to complete wP and ddAC without skipped doses, dose modification, or early discontinuation resulting from toxicity.
# Toxicity: Grade 3 to 4 treatment-related toxicities

<table>
<thead>
<tr>
<th></th>
<th>Arm One: control (%)</th>
<th>Arm Two: Control + Bev (%)</th>
<th>Arm Three: Control + Carbo (%)</th>
<th>Arm Four: Control + Bev and Carbo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>12</td>
<td>13</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22</td>
<td>27</td>
<td>56</td>
<td>67</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>3</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7</td>
<td>9</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>12</td>
<td>0</td>
<td>10*</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Hypokalemia</td>
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<td>1</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>2</td>
<td>6</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>12</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>
CALGB 40603 (Alliance) - results

A: Pathologic complete response (pCR) breast (ypT0/is); B: pCR breast/axilla (ypT0/is No)
In stage II to III TNBC, addition of either carboplatin or bevacizumab to NACT increased pCR rates.

Whether this will improve relapse-free or overall survival is unknown.

Further investigation of bevacizumab in this setting is unlikely.

The role of carboplatin could be evaluated in definitive studies, ideally limited to biologically defined patient subsets most likely to benefit from this agent.
Subgroups within triple negative breast cancers (TNBCs) appear to share impaired DNA repair mechanisms with BRCA1/2 germline mutation +ve (gBRCA+); hypothesised to confer sensitivity to platinum.

TNT tested this hypothesis for women with recurrent locally advanced (LABC) metastatic (MBC) gBRCA+ or TNBC.
Carboplatin vs Docetaxel Triple-Negative Trial (TNT)
## TNT study - results

<table>
<thead>
<tr>
<th></th>
<th>Carboplatin (AUC 6)</th>
<th>Docetaxel 100 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=</strong></td>
<td>188</td>
<td>188</td>
</tr>
<tr>
<td>BRCA 1/2 mutation</td>
<td>9%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Age</td>
<td>55.7 years</td>
<td>54.9 years</td>
</tr>
<tr>
<td>Median dose</td>
<td>AUC 5.97 (5.67-6.01)</td>
<td>96.68 mg/m² (87.37-100)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2%</td>
<td>25%*</td>
</tr>
<tr>
<td>Neuropathy (G3-4)</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>ORR</td>
<td>31.4%</td>
<td>35.6%</td>
</tr>
<tr>
<td>PFS (median)</td>
<td>3.1 months</td>
<td>4.5 months</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 2.5 – 4.2 months)</td>
<td>(95% CI: 4.1 – 5.2 months)</td>
</tr>
<tr>
<td>OS (median)</td>
<td>12.4 months</td>
<td>12.3 months</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 10.4 – 15.3 months)</td>
<td>(95% CI: 10.5 – 13.6 months)</td>
</tr>
<tr>
<td>In BRCA 1/2 mutated cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>68%</td>
<td>33.3%</td>
</tr>
<tr>
<td>PFS (median)</td>
<td>6.8 months</td>
<td>3.1 months</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 4.4 – 8.1 months)</td>
<td>(95% CI: 2.4 – 4.2 months)</td>
</tr>
</tbody>
</table>
Carboplatin is associated with better outcomes than docetaxel among women with *BRCA1*/2 mutation–harboring metastatic or recurrent locally advanced breast cancer.

There was no evidence of superior response to carboplatin compared to docetaxel in unselected triple-negative breast cancer,

But patients with *BRCA1* or *BRCA2* mutation experience significantly greater response and progression-free survival with carboplatin than docetaxel.
Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial

- Patients aged 18–70 years
- Previously untreated, histologically confirmed mTNBC
- ECOG PS 0–1
- i.v. every 3 weeks; max 8 cycles
A

Progression-free survival (%)

Number at risk

Cisplatin plus gemcitabine 118 102 71 42 18 11 6 3 2 2 2 1 0 0 0
Paclitaxel plus gemcitabine 118 93 56 23 10 4 3 1 1 1 1 0 0 0 0

HR 0.692 (95% CI 0.523–0.915); p_{superiority}=0.009

B

Overall survival (%)

Number at risk

Cisplatin plus gemcitabine 118 116 99 85 60 43 33 22 15 11 6 2 0 0
Paclitaxel plus gemcitabine 118 115 99 76 57 42 27 15 13 9 4 2 0 0

HR 0.902 (95% CI 0.605–1.344); p_{log-rank}=0.611
Cisplatin plus gemcitabine could be an alternative or even the preferred first-line chemotherapy strategy for patients with metastatic triple-negative breast cancer.
tnAcity: A phase II/III trial of weekly nab-paclitaxel (nab-P) plus gemcitabine (gem) or carboplatin (carbo) versus gem/carbo as first-line treatment for metastatic triple-negative breast cancer (mTNBC)

- tnAcity (triple-negative Albumin-bound paclitaxel combination international treatment study) is a phase 2/3 trial evaluating the efficacy and safety profiles of 2 nab-P combination regimens (with gem or carbo) as first-line treatment for mTNBC, using gem/carbo as a control.
US chair: Denise Yardley EU; co-chair: Nadia Harbeck

Phase II study start: June 2013; Phase II estimated completion (primary analysis): June 2015; Phase III ‘go/no go’ decision: Sep 2015

First-line TNMBC  
Nab-paclitaxel 125 mg/m² + carboplatin AUC 2 QW 2/3 (n = 80)

Nab-paclitaxel 125 mg/m² + gemcitabine 1000 mg/m² QW 2/3 (n = 80)

Carboplatin AUC2 + gemcitabine 1000 mg/m² QW 2/3 (n = 80)

Winner of the 2 phase II nab-paclitaxel arms (n = 275)
Carboplatin AUC2 + gemcitabine 1000 mg/m² QW 2/3 (n = 275)

Continue treatment until PD or unacceptable toxicity

Patients in phase II will not be included in phase III analysis
Ongoing and Upcoming trials

- **Sharma et al. study:**
  - that will evaluate “BRCAness” as a prognostic marker in patients with TNBC treated with adjuvant anthracycline-based chemotherapy.
  - A panel of BRCAness markers will be performed on tumor tissue genomic DNA and RNA taken from tumor tissue samples from 443 patients. Each marker will be evaluated individually and an exploratory analysis performed of interaction between all the markers.
Ongoing and Upcoming trials

- **SWOG phase II study**:  
  - whether the addition of a PARP inhibitor to platinum-based therapy improves progression-free survival for patients with germline *BRCA* mutation–associated breast cancers and sporadic triple-negative breast cancers that express the *BRCA*Aness phenotype.
  
  - Patients with metastatic triple-negative breast cancer and *BRCA* mutation–associated breast cancer will be randomly assigned between cisplatin/vinorelbine with or without veliparib. All patients will have germline *BRCA* testing after randomization and will then be assigned to the *BRCA*-confirmed negative or *BRCA*-confirmed positive group.
Ongoing and Upcoming trials

• **Two upcoming randomized, phase III trials:**
  ▫ involve patients with triple-negative breast cancer who have residual disease after treatment with neoadjuvant chemotherapy.
  ▫ One trial will compare postoperative platinum-based chemotherapy to observation.
  ▫ The other trial, which is in development, will evaluate the efficacy and safety of PD-1 antibody MK-3475 as adjuvant therapy in patients with > 1 cm residual invasive cancer or any positive lymph nodes after neoadjuvant chemotherapy.
Conclusions

- Platinum emerges as an important component of breast cancer treatment.

- Platinum agents are being explored for use in women with triple-negative breast cancer, with most of the insights into their use coming from neoadjuvant trials.

- The goal is to identify biomarkers of benefit for this agent, particularly because it can be associated with substantial toxicity.
Conclusions

- The relationship between *BRCA* defects and triple-negative breast cancer has been established.

- The relationship between *BRCA* defects and triple-negative breast cancer has therapeutic implications.

- *BRCA1* deficient and basal-like cell lines demonstrate unique chemosensitivities
  - greater sensitivity to platinum agents and gemcitabine
  - a lack of selective sensitivity to anthracyclines
  - a decreased sensitivity to taxanes.
Conclusions

• No standard therapy for metastatic TNBC
  ▫ No evidence that one chemotherapy is superior to another
  ▫ Are triple negative breast cancers truly more susceptible to platinum-based vs other chemotherapy (hence TNT)?
  ▫ Which sub-groups benefit most?
  ▫ Is there a difference between cisplatin and carboplatin?
• Most active agents currently licensed for use appear to be:
  ▫ Cisplatin based chemotherapy
  ▫ Chemotherapy + bevacizumab
• Find out BRCA1/2 status and put your patients into clinical trials
  ▫ Entry criteria MUST reflect the natural history of the disease
Thank you for your attention!
General mechanisms of resistance to chemotherapy

- **Mechanisms of resistance:**
  - diminished drug accumulation
  - elevated drug inactivation
  - DNA repair or elevated DNA damage tolerance
  - enhanced expression of anti-apoptotic genes
  - inactivation of the p53 pathway

Mechanisms of Cisplatin resistance

- reduced uptake or increased efflux of platinum compounds via heavy metal transporters,
- cellular compartmentation, detoxification of bioactive platinum aquo-complexes by Sulphur-containing peptides or proteins
- increased DNA repair
- alterations in apoptotic signaling pathways