Triple negative breast cancer
Biology and targeted therapy

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Association between TNBC, BLBC and BRCA1

BRCA1

TNBC

BLBC

10-35 %

up to 45 %

Non-basal-like (in gene expression analyses)

non triple negative

Gluz, Liedtke et al., Ann Onc 2009
A complex and interlinked taxonomy

Association between TNBC, BLBC and BRCA1

- TNBC: IHC/FISH definition used clinically
- Basal-like BC: Gene expression profile
- BRCA1: germline mutations
- Others (claudin-low, special histological subtypes)

Gluz, Liedtke et al., Ann Onc 2009
Current challenges in defining optimal regiments for TNBC

Biological
- Intrinsic heterogeneity within TNBC
- Lack of targeted therapies

Clinical
- Higher risk and lower threshold for therapy
- The question is not yes/no but which CT?

Analytical
- Small number of trials
- Post hoc and subset analysis with lack of power
Prognosis of TNBC

**BCIRG 001: Survival according to Molecular Subtype (IHC)**

- **Median time to distant recurrence**
  - TNBC = 2.6 years
  - Other breast cancer = 5 years
  - $P < 0.0001$

**Figure 3. Survival after a Diagnosis of Breast Cancer.**

TNBC gives rise to visceral metastases

<table>
<thead>
<tr>
<th>SITE OF FIRST RECURRENTENCE</th>
<th>TNBC (N=61)</th>
<th>Other (N=294)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
</tr>
<tr>
<td>Bone only</td>
<td>10</td>
<td>16.4</td>
<td>116</td>
</tr>
<tr>
<td>Risk of bone recurrence entire follow-up HR (95%CI)</td>
<td>0.5 (0.3-1.0)</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Risk bone recurrence 0-5 years follow-up HR (95%CI)</td>
<td>0.9 (0.4-1.8)</td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>Risk of bone recurrence 5 years to end of follow-up HR (95%CI)</td>
<td>0.1 (0.1-0.8)</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Viscera only</td>
<td>39</td>
<td>63.9</td>
<td>122</td>
</tr>
<tr>
<td>Risk of visceral recurrence entire follow-up HR (95%CI)</td>
<td>1.7 (0.9-1.5)</td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Risk bone recurrence 0-5 years follow-up HR (95%CI)</td>
<td>2.3(1.5-3.5)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Risk of bone recurrence 5 years to end of follow-up HR (95%CI)</td>
<td>0.3(0.1-1.2)</td>
<td></td>
<td>0.09</td>
</tr>
</tbody>
</table>
PATTERNS OF RELAPSE
According to Molecular BC Subtype

Smid M Cancer Res 2008
Poor Outcome of Metastatic TNBC
Why targeting TNBC is important?

<table>
<thead>
<tr>
<th>Line of CT</th>
<th>Total</th>
<th>TNBC</th>
<th>ER+</th>
<th>HER2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>205</td>
<td>45 (100%)</td>
<td>102 (100%)</td>
<td>58 (100%)</td>
</tr>
<tr>
<td>2</td>
<td>159</td>
<td>36 (80%)</td>
<td>79 (77%)</td>
<td>44 (76%)</td>
</tr>
<tr>
<td>3</td>
<td>122</td>
<td>26 (58%)</td>
<td>56 (55%)</td>
<td>69 (52%)</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>13 (29%)</td>
<td>38 (37%)</td>
<td>30 (52%)</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>8 (18%)</td>
<td>24 (24%)</td>
<td>24 (40%)</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>6 (13%)</td>
<td>9 (9%)</td>
<td>19 (33%)</td>
</tr>
</tbody>
</table>

Patients with TN Disease Received Fewer Treatments and Stayed on Each Treatment Regimen For A Shorter Interval

Seah et al, ASCO 2012
Prognosis depending on response to (neoadjuvant) chemotherapy

\[
P = 0.001 
\]

\[
P = 0.24 
\]

\[
\text{CHEMO-SENSITIVE} 
\]

\[
\text{CHEMO-RESISTENT} 
\]

Liedtke et al., J Clin Oncol 2008

pCR Rates by Tumor Subtypes

- **HR+**
  - Grade 1: 7
  - Grade 3: 16

- **HER2+ HR+**
  - No Tras: 18
  - Yes Tras: 30

- **HER2+ HR-**
  - No Tras: 31
  - Yes Tras: 50

- **TRIPLE NEG**
  - 34

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Association of pCR and Survival in TNBC

Cortazar et al Lancet 2014
Biology of TNBC
Biology of TNBC – not all TNBC are BLBC and vice versa

Figure 2. Distribution of the intrinsic molecular and pathology-based subtypes within triple-negative and basal-like tumors. Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.
There are 7 identified Triple negative subtypes

These 7 subtypes predict for pCR in neoadjuvant studies but further follow-up is needed to see if they predict long-term outcome

The 7 subtype classification may lead to innovative personalised medicine strategies for TRN breast cancer
Distant Metastasis-free Survival by TNBC subtype

Figure 1A: Distant metastasis-free survival by TNBC subtype

Proportion of patients surviving by days

Figure 1B: Proportion of patients DMFS by days

P = 0.371

P = 0.287

pCR in taxane treated patients
Xenograft tumors derived from subtype specific cell lines show differential therapeutic sensitivity

BASAL like

LAR

Mesenhimal like
LAR

- Triple negative breast cancer is comprised of 6 molecularly distinct subtypes
  - 10% are "Luminal AR" (LAR)
  - LAR express higher levels of AR mRNA vs other TNBC subtypes
  - LAR breast cancers are heavily enriched in hormonally-regulated pathways
  - Luminal AR is more closely related to hormone receptor positive breast cancer (Luminal A and B) than to other subtypes

BL= Basal Like, IM= ImmunoModulatory, ML= Mesenchymal Like, MSL= Mesenchymal Stem-like, LAR= Luminal AR
Abstract #528

The prognostic role of androgen receptor in early-stage breast cancer patients: A meta-analysis

Ivana Božović Spasojević¹, Dimitrios Zardavas¹, Evandro de Azambuja¹, Lieveke Ameye², Christos Sotiriou³, Martine Piccart¹, Marianne Paesmans²

¹Breast Data Centre, Medical Oncology Department, Institut Jules Bordet, Brussels, Belgium
²Data Centre, Institut Jules Bordet, Brussels, Belgium
³Breast Cancer Translational Research Laboratory, Jules Bordet Institute, Brussels, Belgium
Flow chart of the study

**Screening**
- # of studies identified and screened: n= 493
  - # of studies excluded: n= 473

**Eligible**
- # of studies with reported AR status in correlation with clinical outcome: n= 20
  - # of eligible studies excluded: n= 7
    - Insufficient statistical information to estimate survival

**Evaluable**
- # of studies assessed for eligibility: n= 13
  - Total of 6525 patients
## AR Prognostic Impact in all BC Patients

### UNIVARIATE Analysis

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS (12 studies, N=5658)</td>
<td>0.65</td>
<td>0.50-0.76</td>
<td>p&lt;0.001 for both</td>
</tr>
<tr>
<td>OS (12 studies, N=6525)</td>
<td>0.60</td>
<td>0.47-0.78</td>
<td></td>
</tr>
</tbody>
</table>

### MULTIVARIATE Analysis

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS (5 studies, N=3207)</td>
<td>0.37</td>
<td>0.29-0.47</td>
<td>p&lt;0.001 for both</td>
</tr>
<tr>
<td>OS (6 studies, N=4671)</td>
<td>0.44</td>
<td>0.27-0.72</td>
<td></td>
</tr>
</tbody>
</table>
AR Prognostic Impact within different BC subgroups

<table>
<thead>
<tr>
<th>UNIVARIATE analysis</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFS (5 studies, N=2048)</td>
<td>0.52</td>
<td>0.42-0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS (5 studies, N=3047)</td>
<td>0.58</td>
<td>0.47-0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ER-</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFS (2 studies, N=316)</td>
<td>0.33</td>
<td>0.04-2.49</td>
<td>0.45</td>
</tr>
<tr>
<td>OS (3 studies, N=620)</td>
<td>1.38</td>
<td>1.01-1.88</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>HER2+/ER-</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFS (3 studies, N=358)</td>
<td>1.21</td>
<td>0.86-1.7</td>
<td>0.26</td>
</tr>
<tr>
<td>OS (3 studies, N=358)</td>
<td>1.50</td>
<td>1.01-2.22</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Triple negative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFS (5 studies, N=536)</td>
<td>0.52</td>
<td>0.34-0.79</td>
<td>0.002</td>
</tr>
<tr>
<td>OS (4 studies, N=495)</td>
<td>0.49</td>
<td>0.28-0.86</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Targeted therapy
TNBC is highly proliferative and requires extensive angiogenesis to support rapid growth and metastasis

(? Role for bevacizumab)
Neoadjuvant Antiangiogenesis in TNBC (Gepar-V)

663 pts TNBC

P=0.021

Von Minckwitz et al., NEJM 2012
Survival after neoadjuvant antiangiogenesis in TNBC (Gepar V)

EC-Doc  195 / 969
ECB-DocB  202 / 956
Logrank p-value  0.7837

Von Minckwitz et al., Ann Onc 2014
CALGB 40603: Schema – Randomized Phase II

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

Surgery*
XRT*
No Adjuvant Systemic Treatment Planned*

n = 212  n = 221

41% (35% to 48%)  54% (48% to 61%)

44% (38% to 51%)  52% (45% to 58%)

Odds ratio: 1.71  1-sided P = .0029
Odds ratio: 1.36  1-sided P = .0570

Research biopsies if residual tumor
*MD discretion

Sikov et al. JCO 2014
Recurrence-free survival associated with bevacizumab in TNBC (BEATRICE)

- Median duration of follow-up, months: 31.5 (CT, N=1290) vs 32.0 (CT + BEV, N=1301)
- Events, n (%): 205 (15.9%) vs 188 (14.5%) for CT and CT + BEV, respectively
- 3-year IDFS rate, %: 82.7 (CT) vs 83.7 (CT + BEV), (95% CI) (80.5-85.0%) vs (81.4-86.0%)
- Stratified HR: 0.87 (95% CI: 0.72-1.07)
- Log-rank p-value: 0.1810

Source: Cameron et al., SABCS 2012
PARP Inhibitors In Breast Cancer

- Clear activity of PARP inhibitors as single agents in BRCA-associated breast cancer
- Triple negative breast cancer shares many features with BRCA-associated tumors
  - Alterations in x-chromosome inactivation
  - Range of molecular markers
  - Clinical behavior
  - Genomic instability
Multi-center, Randomized Open-label Phase III Registration Trial of Iniparib in mTNBC

Patient Population:
- mTNBC
- 0–2 prior chemo for metastatic TNBC
- Stable CNS metastases allowed

Stratification:
- No prior chemo vs 1–2 prior chemo for mTNBC

Endpoints:
- Primary: OS, PFS
- Secondary: ORR, safety/tolerability

96% (n=152) of progressing patients crossed over to GCI at time of primary analysis

O’Shaughnessy et al, ASCO 2011

Efficacy Endpoints – ITT Population

Crossover allowed to GCI following Disease Progression* (central review)

Gem/Carbo + Iniparib (GCI) (N= 281)
- Gemcitabine - 1000 mg/m^2 IV d 1, 8
- Carboplatin - AUC2 IV d 1, 8
- Iniparib - 5.6 mg/kg IV d 1,8,11
  21-day cycles

O’Shaughnessy et al, ASCO 2011
Efficacy of Olaparib (Phase-II data)

BRCAness sufficient for synthetic lethality uncommon in advanced non-BRCA TNBC?

BRCA1 methylation present in 80% TNBC

23 treated patients with target lesions identified at baseline
22 had at least one follow-up assessment
1 patient had no follow-up tumour size assessment
- 1 due to missing / incomplete post-baseline assessments

K Gelmon et al Lancet Oncology 2011

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Efficacy of Veliparib (I-Spy II)
Efficacy of Veliparib (I-Spy II)

All HER2-

TNBC

Estimated pCR rate: 22%
95% Probability Interval: 10% to 35%

Estimated pCR rate: 33%
95% Probability Interval: 23% to 43%

Estimated pCR rate: 26%
95% Probability Interval: 11% to 40%

Estimated pCR rate: 52%
95% Probability Interval: 35% to 69%

Probability V+C is superior to Control = 0.92

Probability V+C is superior to Control = 0.99

Rugo et al., SABCS 2012
OlympiA
Olaparib in Adjuvant
BRCAm breast cancer

Post neoadjuvant gBRCA
TNBC, Non-PathCR pts

Restricted to Germline Mutation carriers

Olaparib
300 mg bd
12 month duration

Randomise 1:1
Double blind
N=1320

IDFS

Placebo
12 month duration

Distant DFS, OS

Post adjuvant gBRCA
TNBC
T2 or N+

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Identification of Human TNBC Subtypes

Basal-like 1: Cell cycle, DNA repair and proliferation genes

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

IM: Immune cell processes (medullary breast cancer)

M: Cell motility and differentiation, EMT processes

MSL: Similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features


PARPi, ± DNA damaging agents homologous recombination deficiency assay (BRCA-1 ness)

EGFR (cetuximab, lapatinib) Self-renewal pathways (stem cell) Wnt Notch (PF03084014, AACR 2012)

Immune check point PD1/PDL1, CTLA4 Vaccines: MUC1, NYO-ESO1

Plus PI3Ki, RAS/MEK/Erk, MET, PTEN etc, etc

Agents targeting androgen receptor (enazalutamide, bicalutamide, etc)
Conclusions

1. Inter and intra-tumoral heterogeneity of TNBC, may explain, at least in part, disappointing results from early trials with targeted agents in unselected TNBC.

2. PARP inhibition show promising efficacy in early stage clinical trials, however phase III trials are still lacking.

3. The absence of known predictive factors for bevacizumab efficacy renders recommendations on its use difficult.

4. Novel trials are underway with different targeted agents, PD1 pathway, antiandrogen
Thank you for your attention!

Institute for Oncology and Radiology of Serbia
Daily ChemoTherapy hospital
Pasterova 14, Belgrade

ivanabozovic@outlook.com
ivanabs@ncrc.ac.rs
Chemotherapy
TNBC Ductal

Should the regimen for TNBC phenotype contain anthracyclines and taxanes?
  92.3/2.6/5.1

Should a platinum based regimen be considered?
  • In all patients with TNBC? 7.1/92.9/0
  • Only when known BRCA mutation? 57.9/36.8/5.3

Should dose-dense ChT requiring growth factor support be preferred?
  45/52.5/2.5

Is anthracyclines followed by taxanes an acceptable regimen for BRCA mut TNBC?
  Yes 77.8%, no 11.1%, abstain 11.1%
Back-up
# Bevacizumab in MBC

<table>
<thead>
<tr>
<th></th>
<th>E2100¹</th>
<th>AVADO²</th>
<th>RIBBON-1: Capecitabine³</th>
<th>RIBBON-1: A/T³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (Pl) controlled</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Weekly paclitaxel (P)</td>
<td>q 3 wk docetaxel (D)</td>
<td>Capecitabine (C)</td>
<td>q 3 wk docetaxel/nabPAC/FAC/EC/EC/FEC</td>
</tr>
<tr>
<td>Dose of bevacizumab (B)</td>
<td>10 mg/kg q 2 wk</td>
<td>7.5 or 15 mg/kg q 3 wk</td>
<td>16 mg/kg q 3 wk</td>
<td>15 mg/kg q 3 wk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>P+B</th>
<th>D+PI</th>
<th>D+B</th>
<th>C+PI</th>
<th>C+B</th>
<th>A/T+PI</th>
<th>A/T+B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>25%</td>
<td>49%</td>
<td>49%</td>
<td>55%/63%</td>
<td>24%</td>
<td>35%</td>
<td>38%</td>
<td>51%</td>
</tr>
<tr>
<td>PFS, months</td>
<td>5.9</td>
<td>11.8</td>
<td>80</td>
<td>8.7/8.8</td>
<td>5.7</td>
<td>8.6</td>
<td>8.0</td>
<td>9.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.60</td>
<td>P&lt;.0001</td>
<td>0.79 (7.5 mg)</td>
<td>P = .0318</td>
<td>0.72 (15 mg)</td>
<td>P = .0099</td>
<td>0.69</td>
<td>P = .0002</td>
</tr>
<tr>
<td>OS, months</td>
<td>25.2</td>
<td>26.7</td>
<td>NR</td>
<td>NR</td>
<td>21.2</td>
<td>29</td>
<td>23.8</td>
<td>25.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.88</td>
<td>P = .16</td>
<td>0.92 (7.5 mg)</td>
<td>P = .86</td>
<td>0.86 (15 mg)</td>
<td>P = .27</td>
<td>0.85</td>
<td>P = .83</td>
</tr>
</tbody>
</table>

---

Meta-Analysis (O'Shaughnessy et al ASCO 2010)

**PFS:** 2.5 months, **OS:** 0.3 months

### Progression Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Gem-Carbo N=62</th>
<th>Iniparib + Gem-Carbo N=61</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>3.6 (2.6, 5.2)</td>
<td>5.9 (4.5, 7.2)</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.59 (0.39, 0.9)</td>
<td></td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.012</td>
<td></td>
</tr>
</tbody>
</table>

### Overall Survival - Exploratory

<table>
<thead>
<tr>
<th></th>
<th>Gem-Carbo N=62</th>
<th>Iniparib + Gem-Carbo N=61</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS, months</strong></td>
<td>7.7 (6.5, 13.3)</td>
<td>12.3 (9.8, 21.5)</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.57 (0.26, 0.99)</td>
<td></td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.014</td>
<td></td>
</tr>
</tbody>
</table>

*P-values were not adjusted for multiple interim analyses.*
PD-1 Pathway and Immune Surveillance

- PD-1 is expressed primarily on activated T cells\(^1\)
- Binding of PD-1 to its ligands PD-L1 and PD-L2 impairs T-cell function\(^1\)
- PD-L1 is expressed on tumor cells and macrophages\(^2\)
- Tumors can co-opt the PD-1 pathway to evade immune surveillance\(^2\)
A Phase Ib Study of Pembrolizumab (MK-3475, anti-PD-1 Ab) in Patients With Advanced Triple-Negative Breast Cancer. Nanda et al.

**KEYNOTE-012:**
Triple-Negative Breast Cancer Cohort

- **Recurrent or metastatic ER/PR/HER2-negative breast cancer**
- **ECOG PS 0-1**
- **PD-L1** tumor<sup>a</sup>
- **No systemic steroid therapy**
- **No autoimmune disease (active or history of)**
- **No active brain metastases**

- **Pembrolizumab (Pembro)**
  - **10 mg/kg Q2W**

- **Complete Response**
  - **Discontinuation Permitted**

- **Partial Response or Stable Disease**
  - **Treat for 24 months or until progression or intolerable toxicity**

- **Confirmed Progressive Disease<sup>b</sup>**
  - **Discontinue**

- **PD-L1 positivity:** 58% of all patients screened had PD-L1-positive tumors
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

- **PD-L1 positivity:** 58% of all patients screened had PD-L1-positive tumors
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1
Best Overall Response
(RECIST v1.1, Central Review)

<table>
<thead>
<tr>
<th></th>
<th>Patients Evaluable for Response(^a) n = 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
</tr>
<tr>
<td>Complete response(^b)</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Partial response(^b)</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (44.4%)</td>
</tr>
<tr>
<td>No assessment(^c)</td>
<td>3 (11.1%)</td>
</tr>
</tbody>
</table>

Time to and Durability of Response
(RECIST v1.1, Central Review)

- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response\(^d\): not reached (range, 15 to 40+ weeks)
- PFS 1.9 ms; 6 ms PFS- 23%
• Bevacizumab beyond progression
  – TANIA  
    *(von Minckwitz et al, Lancet Oncol 2014)*

• Maintenance with capecitabine and bevacizumab following response to Bevacizumab
  • IMELDA *(Gligorov et al, Lancet Oncol 2014)*

• Olaparib in BRCA mutated
  • Kaufman B et al, J Clin Oncol epub 03/Nov/2014
Conclusions

- TNBC has significant sub-populations with defective DNA repair
- Defects in HR repair can engender platinum or PARP sensitivity
- Relative efficacy of platinums or PARP inhibitors to standard of care therapies in TNBCs is still emerging needs to take account of diversity within TNBC
- Identification of BRCA1/2 mutation is the current clearest diagnostic of an HRD defect but others are being investigated and reported at this meeting
- Platinums look very active in BRCA1 / BRCA2 mutation carriers
- No published randomised comparison of platinum with standard of care in this group – TNT Trial will report Thursday am S3-01
- Window and high risk post-neoadjuvant residual disease trials testing novel therapy in tumour genome triaged groups eg. BRCAmut will be informative

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### Association between pCR and OS for several therapeutic agents

<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Benefit in neoadjuvant trials</th>
<th>Benefit in adjuvant trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of <strong>taxane</strong> (to anthracycline)</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Addition of <strong>trastuzumab</strong> (to chemotherapy)</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Addition of <strong>bevacizumab</strong> (to chemotherapy)</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Addition of <strong>lapatinib</strong> (to chemotherapy and trastuzumab)</td>
<td>(Y)</td>
<td>N</td>
</tr>
<tr>
<td>Addition of <strong>pertuzumab</strong> (to chemotherapy and lapatinib)</td>
<td>Y</td>
<td>?</td>
</tr>
<tr>
<td>Addition of <strong>platinum</strong> (to neoadjuvant anthracycline/taxane)</td>
<td>Y</td>
<td>?</td>
</tr>
</tbody>
</table>
Neoadjuvant Carboplatin for TNBC (GeparSixto)

Von Minckwitz et al., Lancet Oncol 2014
pCR (ypT0 ypN0) in all Patients with TNBC

<table>
<thead>
<tr>
<th>gBRCA/RAD alteration</th>
<th>no (N=250)</th>
<th>yes (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no (N=193)</td>
<td>40.4% (69/171)</td>
<td>45.5% (10/22)</td>
</tr>
<tr>
<td>yes (N=101)</td>
<td>44.3% (35/79)</td>
<td>63.6% (14/22)</td>
</tr>
</tbody>
</table>

von Minckwitz et al, J Clin Oncol 32:5s, 2014 (suppl; abstr 1005)
Neoadjuvant Carboplatin for TNBC (CALBG 40603 / ALLIANCE)

Sikov et al., JCO 2014
Improving Patient Selection
A Post Neo-adjuvant Umbrella Trial Platform?
PHOENIX

New Diagnosis
Neoadjuvant Rx

Relapse
Vs
No Relapse

Definitive Surgery

Molecular Profiling of the Residual Disease of Triple-Negative Breast Cancers after Neoadjuvant Chemotherapy Identifies Actionable Therapeutic Targets

Balko et al Cancer Discovery 2014
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Tumor-infiltrating lymphocytes are linked to chemotherapy response and prognosis in breast cancer

Lymphocyte-predominant breast cancer (LPBC)
more than 60% TILs

Immunosuppressive regulators:
PD1, PDL1,
CTLA4, IDO1, FOXP3

Immune activation:
T-Cells: CD8A, CCL5
B-Cells: IGKC, CD21,
CD80
Chemoattractants:
CXCL9, CXCL13

Denkert et al, J Clin Oncol 32:5s, 2014 (suppl; abstr 510)
CALGB 40603: Schema – Randomized Phase II

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

Surgery*
XRT*

No Adjuvant Systemic Treatment Planned*

Research biopsies if residual tumor
*MD discretion

pCR Breast (ypT0/is N any) +/− Carboplatin

46% (40-53%) 60% (54-66%)

Odds Ratio: 1.76
p = 0.0018

No Carboplatin
Carboplatin

N=212
N=221
Patients with operable HER2-BC Chemo-naïve & primary tumors ≥2cm

N = 1206

Neoadjuvant Bevacizumab in HER2 - BC Phase III

End points: pCR rate

AC, Adriamycin and cyclophosphamide

Study dosing: q3w (4 cycles Docetaxel + 4 cycles AC)

- Bevacizumab
  - Docetaxel → AC

- Docetaxel → AC

- Bevacizumab
  - Xeloda + Docetaxel → AC

- Xeloda + Docetaxel → AC

- Bevacizumab
  - Gemcitabine + Docetaxel → AC

- Gemcitabine + Docetaxel → AC

Bevacizumab q3 wk x 10

Early signal in HR+

- Bevacizumab regimens
- Docetaxel-AC

*pCR = breast + LN

<table>
<thead>
<tr>
<th>Subtype</th>
<th>All BC</th>
<th>ER+</th>
<th>ER-</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR* (%)</td>
<td>34.5</td>
<td>23.3</td>
<td>47.3</td>
</tr>
<tr>
<td>N=1180</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Bevacizumab regimens: 28.4% (p=0.027)
- Docetaxel-AC: 51.3% (P=0.44)

* pCR = breast + LN
A Note of CAUTION

Which is correct?

GeparQuinto Bevacizumab achieves higher pCR rates in TNBC

NSABP-40 Bevacizumab achieves higher pCR rates in ER+
TNT Trial design
Tutt et al

ER+, PgR-/unknown & HER2- or known BRCA1/2
Metastatic or recurrent locally advanced

Exclusions include:
• Adjuvant taxane in ≤12 months
• Previous platinum treatment
• Non-anthracyclines for MBC

A Priori subgroup analyses:
• BRCA1/2 mutation
• Basal-like subgroups (PAM50 and IHC)
• Biomarkers of HRD

Carboplatin (C)
AUC 6 q3w, 6 cycles
On progression, crossover if appropriate

Docetaxel (D)
100mg/m² q3w, 6 cycles
On progression, crossover if appropriate

n=376
BRCA1/2 = 9%/12%

Carboplatin (C)
AUC 6 q3w, 6 cycles
Docetaxel (D)
100mg/m² q3w, 6 cycles
Objective response

Randomised treatment - all patients (N=376)
- Carboplatin: 59/188 (31.4%)
- Docetaxel: 67/188 (35.6%)

Absolute difference (C-D): -4.2% [95% CI: -13.7 to 5.3]
Exact p = 0.44

Crossover treatment - all patients (N=182)
- Carboplatin (Crossover=Docetaxel): 21/92* (22.8%)
- Docetaxel (Crossover=Carboplatin): 23/90 (25.6%)

Absolute difference (D-C): -2.8% [95% CI: -15.2 to 9.6]
Exact p = 0.73

*Denominator excludes those with no first progression and those not starting crossover treatment

Tutt, SABCS 2014
Progression-free survival

Tutt, SABCS 2014

Median PFS:
- Carboplatin: 3.1 mths (95% CI = 2.5 to 4.2)
- Docetaxel: 4.5 mths (95% CI = 4.1 to 5.2)

Restricted mean survival to 15 mths:
- Carboplatin: 4.8 mths
- Docetaxel: 5.2 mths

Absolute difference:
-0.4 (95% CI -1.1 to 0.3)

p = 0.29

Number of events/at risk

|   | C: 0/188 | 90/98 | 40/56 | 32/22 | 9/13 | 5/8 | 0/7 |
|   | D: 0/188 | 57/130 | 60/69 | 48/20 | 7/13 | 6/5 | 22/3 |
Overall survival

Tutt, SABCS 2014

Median OS:
- Carboplatin: 12.4 mths (95% CI = 10.4 to 15.3)
- Docetaxel: 12.3 mths (95% CI = 10.5 to 13.6)

Restricted mean survival to 15 mths:
- Carboplatin: 10.7 mths
- Docetaxel: 10.8 mths

Absolute difference:
-0.2 (95% CI -1.1 to 0.8)
\[ p = 0.31 \]

<table>
<thead>
<tr>
<th>Number of events/at risk</th>
<th>C: 0/188</th>
<th>23/165</th>
<th>18/141</th>
<th>24/114</th>
<th>22/89</th>
<th>14/71</th>
<th>22/44</th>
</tr>
</thead>
<tbody>
<tr>
<td>D: 0/188</td>
<td>11/176</td>
<td>20/151</td>
<td>35/110</td>
<td>19/85</td>
<td>23/58</td>
<td>26/39</td>
<td></td>
</tr>
</tbody>
</table>
Objective response – BRCA 1/2 status

Germline BRCA 1/2 Mutation (n=43)

- Carboplatin: 17/25 (68.0%)
- Docetaxel: 6/18 (33.3%)

Absolute difference (C-D)
- Carboplatin: 34.7% (95% CI 6.3 to 63.1)
- Docetaxel: Exact p = 0.03

No Germline BRCA 1/2 Mutation (n=273)

- Carboplatin: 36/128 (28.1%)
- Docetaxel: 53/145 (36.6%)

Absolute difference (C-D)
- Carboplatin: -8.5% (95% CI -19.6 to 2.6)
- Docetaxel: Exact p = 0.16

Interaction: randomised treatment & BRCA 1/2 status: p = 0.01

Tutt, SABCS 2014
What About Bevacizumab?

<table>
<thead>
<tr>
<th></th>
<th>Non-bevacizumab (n = 1,008)</th>
<th>Bevacizumab (n = 1,439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>26.4</td>
<td>26.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.97 (0.86–1.08)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>P</em> = .55</td>
</tr>
<tr>
<td>1-year OS rate, %</td>
<td>77</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>P</em> = .003</td>
</tr>
</tbody>
</table>

Number at risk:
- Non-bevacizumab: 1008 (892, 746, 621, 426, 178, 51, 19, 8)
- Bevacizumab: 1439 (1333, 1127, 916, 591, 204, 55, 23, 8)

## First-Line Bevacizumab (E2100, AVADO, Ribbon-1, n = 2447): Subset Analyses

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, months</th>
<th>Median OS, months</th>
<th>1-year OS diff</th>
<th>OS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PFS HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PFS HR</strong></td>
<td><strong>Non-BEV</strong></td>
<td><strong>BEV</strong></td>
<td><strong>Non-BEV</strong></td>
<td><strong>BEV</strong></td>
</tr>
<tr>
<td>TNBC (n = 621)</td>
<td>0.63 (0.52-0.76)</td>
<td>8.1</td>
<td>5.4</td>
<td>18.9</td>
</tr>
<tr>
<td>Prior (neo) adjuvant</td>
<td>0.54 (0.44-0.67)</td>
<td>9.2</td>
<td>6.0</td>
<td>26.7</td>
</tr>
<tr>
<td>taxane (n = 558)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNBC and prior taxane</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>25.6</td>
</tr>
</tbody>
</table>

First-Line Chemotherapy ± Bevacizumab Overall Survival (TNBC, Taxane Pretreated)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab combined with taxane</td>
<td>25.6</td>
</tr>
<tr>
<td>(n = 69)</td>
<td></td>
</tr>
<tr>
<td>Taxane alone</td>
<td>15.0</td>
</tr>
<tr>
<td>(n = 52)</td>
<td></td>
</tr>
</tbody>
</table>

Unstratified hazard ratio (95% CI): 0.61 (0.40–0.94), P = .0247

# Efficacy Data From First-Line Studies With Bevacizumab in TNBC

<table>
<thead>
<tr>
<th>Trial</th>
<th>ORR</th>
<th>PFS, months</th>
<th>HR – PFS/95% CI</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TURANDOT (n = 130)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel + BEV</td>
<td>49%</td>
<td>9.0</td>
<td>1.37 (0.93-2.0)</td>
<td>78 (1 year)</td>
</tr>
<tr>
<td>Capecitabine + BEV</td>
<td>19%</td>
<td>5.6</td>
<td></td>
<td>63 (1 year)</td>
</tr>
<tr>
<td>ATHENA (n = 585)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49%</td>
<td>7.2</td>
<td>(6.6-7.8) months</td>
<td>18.3 months (16.4-19.7)</td>
<td></td>
</tr>
<tr>
<td>CALGB 40502 (n = 218)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nab-paclitaxel + BEV</td>
<td>≈ 7</td>
<td>0.93 (P = .74)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel + BEV</td>
<td>≈ 7</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Ixabepilone + BEV</td>
<td>≈ 5</td>
<td>1.46 (P = .06)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>AVAREG (n = 106)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel + BEV</td>
<td>8.3</td>
<td>(7.8-8.8) months</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>


Some of these agents may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.
Olaparib in MBC: Patients With BRCA1/2 Mutations

![Graph showing tumor shrinkage with Olaparib 400 mg bid and Olaparib 100 mg bid]

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Olaparib 400 mg bid (n = 27)</th>
<th>Olaparib 100 mg bid (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>11 (41%)*</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>10 (37%)</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>PFS</td>
<td>5.7 months</td>
<td>3.8 months</td>
</tr>
</tbody>
</table>


*This agent may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.
# Olaparib in Ovarian and TNBC

## Table: Responses to Olaparib

<table>
<thead>
<tr>
<th>Status</th>
<th>Responses</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer</td>
<td>BRCA1/2</td>
<td>7/17</td>
</tr>
<tr>
<td>Non-BRCA</td>
<td>11/46</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>BRCA1/2</td>
<td>0/8</td>
</tr>
<tr>
<td>Non-BRCA</td>
<td>0/15</td>
<td></td>
</tr>
</tbody>
</table>


This agent may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.
PARPi in Combination?

Phase II study
veliparib (ABT-888) + temozolomide

Phase I study
olaparib + paclitaxel

Phase I study
olaparib + cisplatin

ORR 7% but 38% in BRCA1/2 carriers

<table>
<thead>
<tr>
<th>Paclitaxel 90 (D1,8,15) + olaparib</th>
<th>Cohort 1 n = 9 (no G-CSF)</th>
<th>Cohort 2 n = 10 (G-CSF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Unconfirmed PR</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

"Olaparib in combination with cisplatin 75 mg/m(2) was not considered tolerable"

"Promising antitumor activity in patients with germline BRCA1/2 mutations was observed"

These agents may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.
What Is the Prevalence of BRCA1 Mutation in Patients With TNBC?

Approximately 10%-30%

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>141</td>
<td>20 (14)</td>
<td>Unselected</td>
<td>Bilateral and/or family history of breast cancer</td>
<td>Collins et al (2002)</td>
</tr>
<tr>
<td>74</td>
<td>9 (9)</td>
<td>Selected</td>
<td>Seen in Genetic clinics and underwent BRCA testing</td>
<td>Zhang et al (2011)</td>
</tr>
<tr>
<td>57</td>
<td>22 (39)</td>
<td>Selected</td>
<td>Ashkenazi Jewish heritage; Test for founder mutations</td>
<td>Ashley et al (2006)</td>
</tr>
<tr>
<td>57</td>
<td>12 (16)</td>
<td>Unselected</td>
<td>Ashkenazi Jewish heritage; Test for founder mutations</td>
<td>Gonzalez-Angulo et al (2011)</td>
</tr>
<tr>
<td>64</td>
<td>15 (30)</td>
<td>Selected</td>
<td>TN &lt; 40 years</td>
<td>Comer et al (2011)</td>
</tr>
<tr>
<td>63</td>
<td>8 (13)</td>
<td>Selected and unselected</td>
<td>TN &lt; 40 years and did not qualify for testing according to ASCO guidelines</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

“For now, perhaps the simplest recommendation is to test women under age 50 years with triple-negative breast cancer and women with a family history of early-onset breast cancer or ovarian cancer” Steven Narod JCO

Tesaro Trial in **BRCA1 / BRCA2** Carriers With Advanced Breast Cancer

- **BRCA1 / BRCA2** carriers
- Advanced taxane pretreated breast cancer

- **Niraparib**
- Treatment of physicians choice

**R**
Conclusions: Treatment of TNBC

- 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
What have we learned?

- Carboplatin increases pCR in TNBC
- Best incremental benefit in patients with alteration and family history (pCR rate 64%)
- Little gain from Carbo if no risk factors
- We are ready to incorporate Carbo in neoadjuvant setting for TNBC (...adjuvant for TNBC? Not yet...)
- 15% of TNBC carry a BRCA alteration
- Immunological factors in breast cancer are linked to response to neoadjuvant chemotherapy
Neoadjuvant results with bevacizumab…
very confusing…and probably not helpful
D.F.S. by pCR in Gepartrio

Luminal A
- pCR (ypT0 ypN0) (N=30)
- No pCR (N=172)
Hazard ratio, 1.01 (95% CI, 0.41 to 2.46)
P=0.985 log rank test

Luminal B
- pCR (ypT0 ypN0) (N=20)
- No pCR (N=172)
Hazard ratio, 3.74 (95% CI, 1.15 to 12.1)
P=0.018 log rank test

Triple negative
- pCR (ypT0 ypN0) (N=113)
- No pCR (N=229)
Hazard ratio, 6.67 (95% CI, 3.61 to 11.9)
P=0.001 log rank test

Luminal B HER2+
- pCR (ypT0 ypN0) (N=27)
- No pCR (N=254)
Hazard ratio, 0.89 (95% CI, 0.38 to 2.06)
P=0.775 log rank test

HER2+ (nonLuminal)
- pCR (ypT0 ypN0) (N=50)
- No pCR (N=128)
Hazard ratio, 6.24 (95% CI, 2.25 to 12.1)
P=0.001 log rank test
pCR and Prognosis by Subtype
(N = 4193)

Good news and bad news in TNBC

- **Bad news** – if tumors remain following primary therapy, relapse is highly likely or even inevitable – it is the time taken for the resistant clone(s) to re-populate the tumor.

- **Good news** – there may only be a few critical drivers for each tumor – if we can target these pathways early on, and all at the same time, we maybe able to kill off all the driver clones and cure the patient....
Conclusions and future directions for TNBC

• Bespoke medicine is the future
• The first step is knowledge of the person’s genome and the tumor genome TOGETHER, but there are many more steps
• Knowledge has expanded enormously with NGS
• But there is a fairly substantial gap between knowledge and application
• There are some successes - but no cures – from genomic based-personalized cancer therapy
• It is likely that multi-targeted therapy will be required
Therapy in TNBC subgroup

N=315 centrally confirmed TNBC

PM

Surgery

R

PMCb

Paclitaxel 80 mg/m² q1w

Non-pegylated liposomal doxorubicin (M) 20 mg/m² q1w

Carboplatin AUC 1.5-2 q1w

Bevacizumab 15 mg/kg q3w
Bevacizumab

GeparQuinto

PCR with or without Bevacizumab
(no invasive/non-invasive residual in breast & nodes based on central pathology report review)

Primary endpoint: IDFS

von Minckwitz G et al, NEJM 2012
Cameron D et al, SABCS 2012
Neoadjuvant chemotherapy ± bevacizumab in triple-negative breast cancer

Bear HD, et al. NEJM 2012:366;310-320
Platinum-based neoadjuvant chemotherapy for triple-negative breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Regimen</th>
<th>No. Patients</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byrski et al. JCO 2010</td>
<td>BRCA1+</td>
<td>CMF</td>
<td>14</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC</td>
<td>23</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FAC</td>
<td>28</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT</td>
<td>25</td>
<td>8%</td>
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<tr>
<td></td>
<td></td>
<td>CDDP</td>
<td>12</td>
<td>83%</td>
</tr>
<tr>
<td>Stroh et al. Ann Oncol 2008</td>
<td>TN</td>
<td>ECisF</td>
<td>17</td>
<td>(17%)</td>
</tr>
<tr>
<td>Silver et al. JCO 2010</td>
<td>TN</td>
<td>Cisplatin</td>
<td>28</td>
<td>21%</td>
</tr>
<tr>
<td>Ryan et al. Proc ASCO 2009</td>
<td>TN</td>
<td>Cisplatin + Bev</td>
<td>51</td>
<td>16%</td>
</tr>
</tbody>
</table>
Carboplatin vs Docetaxel
Triple-Negative Trial (TNT)

ER-, PR- and HER2-
1st metastatic relapse
(or inoperable and recurrent locally advanced)

RANDOMISE
1:1

Carboplatin
AUC 6 q3w
6* cycles

Upon imaging confirmed progression**

Docetaxel
100mg/m²
5* cycles

Objective Response
Time to Progression
Objective Response (2nd line protocol therapy)
Time to Treatment Failure
Toxicity
Overall Survival

Docetaxel
100mg/m²
6* cycles

Upon imaging confirmed progression**

Carboplatin
AUC 6 q3w
6* cycles

Optional biological studies

Primary Block
Array CGH/expression array/TMA

and where feasible
Relapse site
Core Biopsy
Array CGH/expression array/TMA

Pl Andrew Tutt
tnAcity: Study Design

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)

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

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

Patients in phase II will not be included in phase III analysis

Continue treatment until PD or unacceptable toxicity
CTNeoBC: the “ΔΔ” dilemma

Triple Negative

Event-Free Survival Probability

HR=0.24, P<0.001

pCR (n=389) vs no pCR (n=768)

A perfect scenario example (simulated-data)

Triple negative subgroup

P Cortazar, US FDA, SABCS 2012
Biology of TNBC – what is new?
Proposed algorithm of stratification of triple-negative tumors.

Abbreviations: EGFR, epidermal growth factor receptor; PARP, poly (ADP-ribose) polymerase.
Basal-like 1 (BL1): cell-cycle, proliferation and DNA damage response genes
Basal-like 2 (BL2): growth factor signaling (EGF, MET, Wnt/β-catenin, IGF 1R)
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)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Subtypes of TNBC based on gene expression profiling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtype</td>
<td>Gene expression profile</td>
</tr>
<tr>
<td>Basal-like 1</td>
<td>High expression of genes involved in cell cycle progression, cell division and DNA damage response pathways</td>
</tr>
<tr>
<td>Basal-like 2</td>
<td>High expression of genes involved in cell cycle progression, cell division and growth factor signaling</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>High expression of genes involved in immune processes</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>High expression of genes involved in motility and extracellular matrix</td>
</tr>
<tr>
<td>Mesenchymal stem-like</td>
<td>High expression of genes involved in motility, extracellular matrix and growth factor signaling</td>
</tr>
<tr>
<td>Luminal androgen receptor</td>
<td>High expression of genes involved in hormonally regulated pathways</td>
</tr>
</tbody>
</table>

Elsamany et al. Med Oncol 2014
## Meta-analysis

### Meta-Analysis: Progression-Free Survival With Bevacizumab-Containing Therapy

<table>
<thead>
<tr>
<th></th>
<th>E2100</th>
<th>AVADO</th>
<th>RIBBON-1 (Capecitabine)</th>
<th>RIBBON-1 (Taxane, Anthra)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-BV</td>
<td>BV</td>
<td>Non-BV</td>
<td>BV</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.8</td>
<td>11.3</td>
<td>8.0</td>
<td>8.8</td>
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<tr>
<td>Hazard Ratio</td>
<td>0.48</td>
<td>0.62</td>
<td>0.69</td>
<td>0.64</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>0.0003</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Meta-Analysis: Overall Survival

<table>
<thead>
<tr>
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<th>E2100</th>
<th>AVADO</th>
<th>RIBBON-1 (Capecitabine)</th>
<th>RIBBON-1 (Taxane, Anthra)</th>
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<tr>
<td></td>
<td>Non-BV</td>
<td>BV</td>
<td>Non-BV</td>
<td>BV</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>26.6</td>
<td>26.7</td>
<td>24.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.97</td>
<td>0.96</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
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</table>
Meta-Analysis: Progression-Free Survival With Bevacizumab-Containing Therapy

![Graph showing progression-free survival](image)

- FDA revoked approval
- EMA kept only for 1st line & only with paclitaxel

Meta-Analysis: Overall Survival

![Graph showing overall survival](image)

Urgent need for:
- PREDICTIVE BIOMARKERS
- Reasonable PRICES for new agents!
Targeting Triple Negative

- **Bevacizumab beyond progression**
  - **TANIA**
    (von Minckwitz et al, Lancet Oncol 2014)

- **Maintenance with capecitabine and bevacizumab following response to Bevacizumab**
  - **IMELDA** (Gligorov et al, Lancet Oncol 2014)

- **Olaparib in BRCA mutated**
  - Kaufman B et al, J Clin Oncol epub 03/Nov/2014
PARP inhibitors

Targeting BRCA 1/2 for tumor selective killing

BRCA1/BRCA2 carrier
normal tissue cells

DNA repair

Homologous recombination (HR repair)

Base excision DNA repair (PARP-dependent)

Few normal tissue effects

HR repair

BRCA1/BRCA2 carrier
Tumor cells

PARP inhibitor

Disables Base excision DNA repair

Specific tumor cell killing

PARP inhibitor

Base excision DNA repair

Tutt A et al. Cold Spring Harb Symp Quant Biol 2005;70:139–146; Slide courtesy Alan Ashworth / Andrew Tutt
TNBC Subtypes: (Some) Research Strategies

Basal-like 1: Cell cycle, DNA repair and proliferation genes
- PARPi, ± DNA damaging agents homologous recombination deficiency assay (BRCA-1 ness)

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)
- EGFR (cetuximab, lapatinib)
- Self-renewal pathways (stem cell)
  - Wnt
  - Notch (PF03084014, AACR 2012)

IM: Immune cell processes (medullary breast cancer)
- Immune check point
  - PD1/PDL1, CTLA4
- Vaccines: MUC1, NYO-ESO1

M: Cell motility and differentiation, EMT processes
- Plus
  - PI3Ki, RAS/MEK/Erk, MET, PTEN etc, etc

MSL: Similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features
- Agents targeting androgen receptor
  - enzalutamide, bicalutamide, etc
Triple negative breast cancer

Enriched in basal-like breast cancer
- Enriched in BRCA1-germline mutations
- High chemosensitivity and high chemoresistance
- High frequency of p53 mutations
  Cytokeratins 5/6, P-catherin, EGFR
Association of pCR and Survival

Event-free Survival

HR = 0.48, P < 0.001

Overall Survival

HR = 0.36, P < 0.001

pCR = ypT0/is ypN0

* Nominal p-value

Cotezar et al, AACR 2013, Lancet 2014
Identification of Human TNBC Subtypes

Basal-like 1: Cell cycle, DNA repair and proliferation genes

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

IM: Immune cell processes (medullary breast cancer)

M: Cell motility and differentiation, EMT processes

MSL: Similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features