Is there a role for new cytotoxic agents in TNBC?

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Disclosures

• Advisor
  – Roche, Novartis, Celgene

• Honoraria
  – Roche, Novartis, Celgene, Eisai
Breast Cancer Diseases – 201…

All Breast Cancers

- ER+ 65-75%
- HER2+ 15-20%
- Triple negative 15%
- HER3+
- IGFR1+
- PI3Kmut 10%
- p95+ 4%
- P53mut 30-40%
- FGFR1 Ampl 8%
- PTENloss 30-50%
- BRCA Mut 8%
- PI3Kmut 10%
- HER2+ 15-20%
- Triple negative 15%

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“Triple Negative” Breast Cancer

Immunohistochemistry

- ER and PR <1% nuclear
- HER2 “negative”: IHC 0 or 1+ staining or 2+ IHC staining with negative FISH

Histology

- High grade ductal
Median Time from Distant Relapse to Death

“Triple Negative” Breast CA
Other Breast CA

TNBC paradox: chemo-sensitive…but relapse more aggressive with worse OS
What is ‘Standard Therapy’ For TNBC?

• No specific systemic regimen guidelines exist

• Little data on which to base decisions

• Few historical controls
  – A challenge to design clinical trials for this subgroup
TNBC: Current Treatment Strategies

- TNBC paradox: chemo-sensitive…but relapse more aggressive with worse OS
- Cannot treat with existing targeted therapies (hormonal therapy or trastuzumab)
- Manage same as other BCs with same grade & stage
- Limited data available from prospective trials in this population
  - Best available data mostly subpopulation analyses
CMTN: Antraciclinas vs. Docetaxel

<table>
<thead>
<tr>
<th></th>
<th>CMTN</th>
<th>HER2</th>
<th>Luminal B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel 100 mg/m² x 4 ciclos</td>
<td>29</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>Doxorubicin 75 mg/m² x 4 ciclos</td>
<td>10</td>
<td>55</td>
<td>16</td>
</tr>
</tbody>
</table>

Single agent Neoadjuvant Chemotherapy study with Doxorubicin or Docetaxel for 4 cycles in Stage II-IIIa (> 3 cm)

pCR rate by phenotype
# Taxanes For Metastatic TNBC?

Retrospective subgroup analyses
Placebo arm data

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>N</th>
<th>Setting</th>
<th>Taxane</th>
<th>Outcome in TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9342¹</td>
<td>III</td>
<td>44</td>
<td>First- or second-line metastatic</td>
<td>Paclitaxel weekly and q3w</td>
<td>ORR = 26% TTF = 2.8 months OS = 8.6 months</td>
</tr>
<tr>
<td>ECOG 2100²</td>
<td>III</td>
<td>110</td>
<td>First-line metastatic</td>
<td>Paclitaxel weekly</td>
<td>ORR = 11.7%⁴ PFS = 5.3 months</td>
</tr>
<tr>
<td>AVADO³</td>
<td>III</td>
<td>52</td>
<td>First-line metastatic</td>
<td>Docetaxel q3w</td>
<td>ORR = 23.1%⁴ PFS = 6.1 months</td>
</tr>
</tbody>
</table>

## Capecitabine For Metastatic TNBC?

### Retrospective subgroup analyses

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>N</th>
<th>Setting</th>
<th>Treatment</th>
<th>Outcome in TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled analysis(^1)</td>
<td>III</td>
<td>208</td>
<td>Third-line or greater metastatic</td>
<td>Capecitabine</td>
<td>ORR = 15% PFS = 1.7 months</td>
</tr>
<tr>
<td>RIBBON-1(^2)</td>
<td>III</td>
<td>50</td>
<td>First-line metastatic</td>
<td>Capecitabine + placebo</td>
<td>PFS = 4.2 months</td>
</tr>
</tbody>
</table>

Poor Outcome of Metastatic TNBC (N=112)

Initial therapy → First distant relapse → First line chemo (Median D.F.I.)

- First distant relapse:
  - 12 weeks
- Time on Treatment:
  - 9 weeks
  - 4 weeks

First line chemo
Second line chemo
Third line chemo

## TNBC: Platinum compounds

<table>
<thead>
<tr>
<th>Study</th>
<th>Platinum</th>
<th>Dosis</th>
<th>N</th>
<th>First Line</th>
<th>ORR(%)</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BALI-1</td>
<td>Cisplatin</td>
<td>75 mg/m² q3w</td>
<td>48</td>
<td>73%</td>
<td>6 (10.3%)</td>
<td>1.5 m</td>
</tr>
<tr>
<td>BSI-201</td>
<td>Carboplatin</td>
<td>AUC 2 d1, 8 q3w 1000 mg/m² d1, 8</td>
<td>62</td>
<td>59%</td>
<td>20 (32%)</td>
<td>3.3 m</td>
</tr>
<tr>
<td>TBCRC 001</td>
<td>Carboplatin</td>
<td>AUC 2 d1, 8, 15 q4w</td>
<td>71</td>
<td>46%</td>
<td>13 (18%)</td>
<td>2.0 m</td>
</tr>
<tr>
<td></td>
<td>Cetuximab</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**References:**

Evolution of Chemotherapy for Metastatic Breast Cancer

Mid 20th century
- Early chemotherapy
- CMF (VP)

Late 20th century
- Anthracyclines
- Vinorelbine

Late 20th century
- Taxanes
- Capecitabine

Early 21st century
- Biological era begins
- Novel antitubulins
- Advanced cytotoxics

CMF = cyclophosphamide + methotrexate + fluorouracil; VP = vincristine + prednisone
Microtubule Targeted Agents for MBC

- **Microtubule destabilizers**: inhibit polymerization, loss of cellular microtubules
  - *New vinca* alkaloids
    - Vinflunine
    - Halichondrins: Eribulin
- **Microtubule stabilizers**: stimulate polymerization, increase density of cellular microtubules
  - Taxanes
    - Paclitaxel, docetaxel, nab-paclitaxel
  - Epothilones
    - Ixabepilone
Monotherapy with nab-Paclitaxel in Taxane-Refractory mBC

No data reported in randomized trials

**PATIENT COHORTS**

- **nab-Paclitaxel 100 mg/m²**
  - qw 3/4
  - n = 106

- **nab-Paclitaxel 125 mg/m²**
  - qw 3/4
  - n = 75

- Study initiated at 100 mg/m² qw 3 of 4 wks
- Protocol amended to include additional cohort of patients to receive 125 mg/m² qw 3 of 4 wks
- Each cohort was analyzed separately
# Monotherapy with nab-Paclitaxel in Taxane-Refractory mBC

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>Total population</td>
<td>16/106 (14%)</td>
</tr>
<tr>
<td>Triple negative population</td>
<td>3/21 (14%)</td>
</tr>
</tbody>
</table>
# Phase II: Ixabepilone for previously treated Anthracycline and Taxane

<table>
<thead>
<tr>
<th></th>
<th>Thomas et al&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Perez et al&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ixabepilone 40 mg/m2 D1 q 21 days</td>
<td>Ixabepilone 40 mg/m2 D1 q 21 days</td>
</tr>
<tr>
<td>Number of patients</td>
<td>49 (taxane-resistant)</td>
<td>126</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>12 (4.7-26.5)</td>
<td>11.5 (6.3-18.9)</td>
</tr>
<tr>
<td>Triple negative population</td>
<td>1/18 (5.6%)</td>
<td>5/42 (12%)</td>
</tr>
</tbody>
</table>

Thomas. JCO 2007; Perez et al. JCO 2007
Ixabepilone phase III Study Designs

Ixabepilone + Capecitabine  VS.  Capecitabine

(1) ER-PR-HER-2-

Yes  187
No  565

(2) ER-PR-HER2-

Yes  0.64 (0.48 to 0.84)
No  0.86 (0.74 to 1.00)

Favors I + C  1.0  Favors C

1Thomas et al. JCO 2007; 2Sparano et al. JCO 2010
Eribulin Mesylate (E7389): A Novel Tubulin Targeted Agent

- Eribulin mesylate (E7389), a non-taxane microtubule dynamics inhibitor with a novel mechanism of action, is a structurally simplified synthetic analog of the marine natural product halichondrin B$^{1,2}$

1. Eribulin suppresses microtubule polymerization\textsuperscript{1}\textsuperscript{t}

2. Eribulin has \textit{no significant effect} on microtubule depolymerization

3. Eribulin sequesters tubulin into non-functional aggregates\textsuperscript{1}

1 Jordan et al. Mol Cancer Ther 2005
## Phase II: Eribulin for previoulsy treated Anthracycline and Taxane Advanced BC

<table>
<thead>
<tr>
<th></th>
<th>Vahdat et al(^1)</th>
<th>Cortes et al(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eribulin 1.4 mg/m2 D1 + 8 q 21 days</td>
<td>Eribulin 1.4 mg/m2 D1 + 8 q 21 days</td>
</tr>
<tr>
<td>Median number of cycles</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>16 (10-25)</td>
<td>9 (6-13)</td>
</tr>
<tr>
<td>Triple negative population</td>
<td>2/27 (7%)</td>
<td>1/54 (2%)</td>
</tr>
</tbody>
</table>

- A/T, anthracycline/taxane; A/T/C, anthracycline/taxane/capecitabine

Vahdat et al. JCO 2009; Cortes et al. JCO 2010
EMBRACE Study Design

Global, randomized, open-label Phase III trial (Study 305)

Patients (n=762)
- Locally recurrent or metastatic breast cancer
- 2-5 prior chemotherapies
  - ≥2 for advanced disease
  - Prior anthracycline and taxane
- Progression on or within 6 months of last chemotherapy
- Neuropathy ≤grade 2
- ECOG ≤2

Eribulin mesylate
1.4 mg/m$^2$, 2-5 min IV bolus
Day 1, 8 q21 days

Treatment of Physician’s Choice (TPC)
Any monotherapy (chemotherapy, hormonal, biological)* or supportive care only†

Stratification
- Geographic region
- Prior capecitabine treatment
- HER2/neu status
ACCRUAL: Nov 2006 – Nov 2008

Cortes et al. Lancet 2011

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# Disease and Tumor Characteristics (ITT)

<table>
<thead>
<tr>
<th></th>
<th>ERIBULIN (n=508) %</th>
<th>TPC (n=254) %</th>
<th>TOTAL (n=762) %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>66.1</td>
<td>67.3</td>
<td>66.5</td>
</tr>
<tr>
<td>–</td>
<td>28.1</td>
<td>28.3</td>
<td>28.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>5.7</td>
<td>4.3</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>PR Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>50.0</td>
<td>48.4</td>
<td>49.5</td>
</tr>
<tr>
<td>–</td>
<td>38.8</td>
<td>40.2</td>
<td>39.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>11.2</td>
<td>11.4</td>
<td>11.3</td>
</tr>
<tr>
<td><strong>HER2 Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>16.3</td>
<td>15.7</td>
<td>16.1</td>
</tr>
<tr>
<td><strong>Triple negative (ER/PR/HER2)</strong></td>
<td>18.3</td>
<td>20.1</td>
<td>18.9</td>
</tr>
<tr>
<td><strong>No. of organs involved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>50.6</td>
<td>46.1</td>
<td>49.0</td>
</tr>
<tr>
<td>&gt;2</td>
<td>49.0</td>
<td>54.0</td>
<td>50.6</td>
</tr>
</tbody>
</table>
Overall Survival

Overall results (n=762)

- Age:
  - <40 (n=51)
  - ≥40 - <65 (n=560)
  - ≥65 (n=151)

- Race:
  - Caucasian (n=703)
  - Non-Caucasian (n=59)

- Receptor status:
  - ER/PR + (n=528)
  - ER/PR - (n=187)
  - Unknown (n=47)

- No. of organs involved:
  - ≤2 (n=537)
  - >2 (n=217)

- Sites of disease:
  - Visceral (n=624)
  - Non-Visceral (n=130)

Based upon a stratified Cox analysis including geographic region, HER2 status, and prior capecitabine therapy as strata
Etirinotecan Pegol: A Tumor-Targeted Topoisomerase I Inhibitor

The large polymer prodrug does not cross normal vasculature efficiently, limiting concentrations in normal tissues.

Hydrolysis of the polymer conjugate releases prodrug.

Active drug affects tumor cell DNA, inducing cell death.

NKTR-102 enters tumor tissue through leaky vasculature.

Over time, natural chemical processes free active drug providing consistent exposure.

Courtesy of Nektar Therapeutics
Phase 2 Study Design: Randomized to Two Schedules of Etirinotecan Pegol (NKTR-102)

- **Primary Efficacy Objective:**
  - Determine the objective response rate (ORR) by RECIST v 1.0
  - Determine the optimal schedule of NKTR-102 in breast cancer

- **Secondary Objectives:** PFS, OS and safety

Metastatic Breast Cancer
N=70 ≤ 2 Regimens for Metastatic Disease

145 mg/m² q21d

145 mg/m² q14d

Primary Endpoint: Objective Response Rate (RECIST)
## Response Rate By Prior Therapy

<table>
<thead>
<tr>
<th>Prior Therapy Subgroup*</th>
<th>Overall Response by RECIST v 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (%)</td>
</tr>
<tr>
<td><strong>Evaluable Patients</strong></td>
<td></td>
</tr>
<tr>
<td><strong>NKTR-102</strong></td>
<td>n/N (%)</td>
</tr>
<tr>
<td>145 mg/m² q14 days</td>
<td>7/22 (32%)</td>
</tr>
<tr>
<td>145 mg/m² q21 days</td>
<td>5/21 (24%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>12/43 (28%)</td>
</tr>
</tbody>
</table>

**Triple Negative**

| 2/8 (25%)              | 5/10 (50%)                        |
| **7/18 (39%)**         |                                  |

**Prior A/T/C**

| 2/6 (33%)              | 3/10 (30%)                        |
| **5/16 (31%)**         |                                  |

- A/T, anthracycline/taxane; A/T/C, anthracycline/taxane/capecitabine
BEACON Study Design

Patients (n=840)
- Locally recurrent or metastatic breast cancer
- 2-5 prior chemotherapies
  – ≥2 for advanced disease
  – Prior anthracycline, taxane and capecitabine

NKTR-102
145 mg/m²
Day 1, q21 days

Treatment of Physician’s Choice (TPC)
Any monotherapy (eribulin, ixabepilone, vinorelbine, gemcitabine, taxanes)

Stratification
- Geographic region
- Prior eribulin treatment
- Triple negative vs HER2+ vs Other
# Other compounds

<table>
<thead>
<tr>
<th></th>
<th>ORR (TNMBC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinflunine</td>
<td>NR\textsuperscript{1,2}</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>NR\textsuperscript{3}</td>
</tr>
<tr>
<td>Larotaxel</td>
<td>NR\textsuperscript{4}</td>
</tr>
</tbody>
</table>

- No data reported in randomized trials

\textsuperscript{1}Fumoleau et al. AJCO 2009; \textsuperscript{2}Campone et al. BJC 2006; \textsuperscript{3}Zelek et al. BJC 2006; \textsuperscript{4}NR\textsuperscript{1,2} Dieras et al. Ann Oncol 2008
Conclusions

• Cytotoxic chemotherapy is the SOC for patients with triple negative MBC

• Very limited efficacy data of new agents in this specific population

• More and better targeted agents should be explored in combination with chemotherapy