Clinical Research on Tubulin Inhibition and Anti-angiogenic Agents in TNBC

Edith A Perez, MD
## Disclosures for Edith A Perez, MD

| Paid Research to Mayo Clinic | Genentech BioOncology, GlaxoSmithKline, Roche Laboratories Inc, sanofi-aventis |

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Key Topics Discussed

• Anti-tubulin agents and TNBC: Taxanes and ixabepilone

• Angiogenesis inhibitors and TNBC: Bevacizumab
CALGB-40603: The Triple-Negative Neoadjuvant Trial (TNNT)

Target accrual = 362

Eligibility

- Stage II-IIIA resectable breast cancer ≥ 1 cm
- HER2-negative (IHC 0-1+ or FISH <2.0); ER-/PR-poor
- Registered on CALGB-150709 correlative tissue study

1. Paclitaxel 80 mg/m² x 12 → Dose Dense (dd) AC x 4

2. Paclitaxel + dd AC as in arm 1; Bevacizumab 10 mg/kg q2wk x 9

3. Paclitaxel + dd AC as in arm 1; Carboplatin AUC 6 q3wk x 4

4. Paclitaxel + dd AC as in arm 1 + Bevacizumab as in arm 2 + Carboplatin as in arm 3

Courtesy of Clifford A Hudis.
Response to Neoadjuvant Therapy and Long-Term Survival in Patients with Triple-Negative Breast Cancer

Liedtke C et al.

### pCR Rates to Neoadjuvant Chemotherapy as a Function of Triple-Negative Status

<table>
<thead>
<tr>
<th>Regimens</th>
<th>pCR Rates</th>
<th></th>
<th>Non-TNBC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>TNBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAC/FEC/AC (n = 308)</td>
<td>8%</td>
<td>20%</td>
<td>5%</td>
<td>0.0001</td>
</tr>
<tr>
<td>TFAC/TFEC (n = 588)</td>
<td>19%</td>
<td>28%</td>
<td>17%</td>
<td>0.0072</td>
</tr>
<tr>
<td>Single-agent taxane (n = 58)</td>
<td>5%</td>
<td>12%</td>
<td>2%</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Patients with TNBC have a higher incidence of pCR to taxane-based regimens.
Breast Cancer Molecular Profiles Predict Tumor Response of Neoadjuvant Doxorubicin and Paclitaxel, the I-SPY TRIAL (CALGB 150007/150012, ACRIN 6657)

Esserman LJ et al. 

*Proc ASCO 2009; Abstract LBA515.*
I-SPY TRIAL: pCR in Context of IHC and Select Molecular Subtypes

<table>
<thead>
<tr>
<th>IHC</th>
<th>pCR (n = 190)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-positive, HER2-negative (n = 91)</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>HR-positive, HER2-positive (n = 23)</td>
<td>32%</td>
<td>NR</td>
</tr>
<tr>
<td>HR-negative, HER2-positive (n = 23)</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>HR-negative, HER2-negative (n = 53)</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene Profile Intrinsic Subtypes</th>
<th>pCR (n = 144)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A or B (n = 72)</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>HER2-enriched (n = 22)</td>
<td>52%</td>
<td>NR</td>
</tr>
<tr>
<td>Basal (n = 48)</td>
<td>34%</td>
<td></td>
</tr>
</tbody>
</table>

Patients with TNBC are responsive to neoadjuvant paclitaxel/doxorubicin x 4.

TNT Trial: A Phase III Trial of Carboplatin versus Docetaxel for Metastatic or Recurrent Locally Advanced TNBC

Target accrual = 400 (open)

Eligibility

- Histologically confirmed ER-, PR-, HER2- primary BC
- Metastatic or locally advanced disease
- ECOG PS 0-2

- Carboplatin = AUC 6 every 3 weeks for six cycles
- Docetaxel = 100 mg/m² every 3 weeks for six cycles
CALGB-40502/NCCTG N063H: A Phase III Trial of Bevacizumab with Paclitaxel, *Nab* Paclitaxel or Ixabepilone in Patients with Stage IIIC-IV Breast Cancer

Target accrual = 900 (open)

**Eligibility**

- Stage IIIC-IV measurable disease ≥ 1 cm by CT scan, or ≥ 2 cm by conventional techniques
- Known ER, PR and HER2 status
- No prior chemotherapy for metastatic disease

1. Paclitaxel 90 mg/m² IV d1, 8 and 15 → **Bevacizumab** d1 and 15 q28 days

2. *Nab* paclitaxel 150 mg/m² IV d1, 8 and 15
   - **Bevacizumab** d1 and 15 q28 days

3. Ixabepilone 16 mg/m² IV d1, 8 and 15 → **Bevacizumab** d1 and 15 q28 days
Phase II Genomics Study of Ixabepilone as Neoadjuvant Treatment for Breast Cancer

Baselga J et al.

**pCR$_{Breast}$ Rates to Neoadjuvant Ixabepilone by Hormone and HER2 Receptor Status**

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Total Patients</th>
<th>Patients w/ Response</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treated patients</td>
<td>161</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>ER-negative</td>
<td>72</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>ER/PR-negative</td>
<td>61</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>ER/PR/HER2-negative</td>
<td>42</td>
<td>11</td>
<td>26</td>
</tr>
</tbody>
</table>

Neoadjuvant ixabepilone is active in various breast cancer subtypes including TNBC.
Ixabepilone plus Capecitabine vs Capecitabine in Patients with Triple Negative Tumors: A Pooled Analysis of Patients from Two Large Phase III Clinical Studies

Rugo HS et al.

Proc SABCS 2008;Abstract 3057.
Capecitabine +/- Ixabepilone: Study Design for CA 163-046 and CA 163-048*

Eligibility
- Locally advanced or metastatic breast cancer (MBC)
- Pretreated or resistant to taxanes and anthracyclines

Ixabepilone (Ixa)
40 mg/m² IV over 3 hr d1 q3wk +
Capecitabine 1,000 mg/m² BID 14 days q3wk

Capecitabine (Cape)
1,250 mg/m² BID 14 days q3wk

* Phase III trials with similar design. Data pooled (n = 443)

Results: Pooled Analysis of Patients with Metastatic TNBC

Median PFS
HR = 0.63 (95% CI, 0.52 to 0.77)  
$p < 0.0001$

Median OS
HR = 0.87 (95% CI, 0.71 to 1.07)  
$p = 0.1802$

Ixa + Cape  
(N = 213 for OS)  
(N = 191 for ORR and PFS)

Cape  
(N = 230 for OS)  
(N = 208 for ORR and PFS)
Conclusions Related to Ixabepilone in Metastatic TNBC

• In the largest clinical data set recorded, Ixa plus Cape in patients with metastatic TNBC resulted in:
  - Prolonged PFS by 2.5 months
  - Doubling of ORR
• Ixa plus Cape did not increase OS compared to Cape alone
• Cape alone offers little benefit for patients with TN MBC previously treated with an anthracycline and a taxane
TITAN Phase III Trial Design

Target accrual = 1,800 (open)

Eligibility
- Histologically confirmed invasive unilateral breast cancer
- Completion of locoregional surgery
- HER2-, PR- and ER-negative

Doxorubicin + Cyclophosphamide
- Doxorubicin = 60 mg/m² q21days x 4
- Cyclophosphamide = 600 mg/m² q21days x 4

Ixabepilone
- Ixabepilone = 40 mg/m² q21days x 4

Paclitaxel
- Paclitaxel = 80 mg/m² weekly x 12

CA163-139 Phase II Trial Design

Target accrual = 80 (closed)

Eligibility

- TN locally advanced non-resectable and/or mBC
- No prior systemic therapy

Ixabepilone
40 mg/m², 3-week cycle

Ixabepilone + Cetuximab
Loading dose 400 mg/m² then 250 mg/m², weekly

- Study will be completed once all subjects have progressed or 15 months after the Last Patient First Visit, which ever comes first
BEATRICE Phase III Trial Design

Target accrual = 2,530 (open)

Eligibility

- Primary invasive breast cancer
- Centrally confirmed as triple negative
- No clinically significant cardiovascular disease

Standard chemotherapy

Standard chemotherapy + Bevacizumab

- **Bevacizumab** = 5 mg/kg/week x 1 year
- **Standard chemotherapy** = anthracycline with or without taxane or taxane only
- **Primary endpoint**: DFS

Comparison of Subgroup Analyses of PFS from Three Phase III Studies of Bevacizumab in Combination with Chemotherapy in Patients with HER2-Negative Metastatic Breast Cancer

O’Shaughnessy J et al.
Proc SABCS 2009;Abstract 207. (Poster)
# Improvement in PFS with Addition of Bevacizumab (B) in E2100, AVADO and RIBBON-1

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>E2100 (n = 722)</th>
<th>AVADO* (n = 736)</th>
<th>RIBBON-1† (n = 1,237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (Hazard Ratio, HR)</td>
<td>5.5 (0.48)</td>
<td>0.8 (0.70); 0.9 (0.61)</td>
<td>2.9 (0.69); 1.2 (0.64)</td>
</tr>
<tr>
<td>Triple-negative (HR)</td>
<td>5.3 (0.49)</td>
<td>0.8 (0.69); 2.8 (0.53)</td>
<td>1.9 (0.72); 0.3 (0.78)</td>
</tr>
<tr>
<td>Neoadjuvant/adjuvant taxane (HR)</td>
<td>7.3 (0.33)</td>
<td>4.2 (0.62); 1.9 (0.43)</td>
<td>4.5 (0.62); 2.4 (0.65)</td>
</tr>
<tr>
<td>Age ≥ 65 (HR)</td>
<td>4.3 (0.67)</td>
<td>0.8 (0.76); 0.8 (0.68)</td>
<td>2.9 (0.69); 1.6 (0.83)</td>
</tr>
</tbody>
</table>

* B 7.5 mg/kg, 15 mg/kg (doses were also used in the other two trials); † Capecitabine/B; Taxane/anthracycline/B
First-Line Bevacizumab Combination Therapy in Triple-Negative Locally Recurrent (LR)/Metastatic Breast Cancer (mBC): Subpopulation Analysis of Study MO19391 (ATHENA) in >2000 Patients

Thomssen C et al.

Proc SABCS 2009;Abstract 6093.
MO19391 (ATHENA) Trial Design

Eligibility (n = 2,251)

<table>
<thead>
<tr>
<th>HER2-negative</th>
<th>Bevacizumab + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior chemotherapy or concomitant endocrine therapy</td>
<td></td>
</tr>
</tbody>
</table>

- **Bevacizumab** = 10 mg/kg q2wks or 15 mg/kg q3wks
- **Chemotherapy** = taxane alone or in combination (clinician’s choice) or standard chemotherapy if taxane not considered standard of care
ATHENA Results: Efficacy (median follow-up 12.7 months)

<table>
<thead>
<tr>
<th></th>
<th>TNBC (n = 577)</th>
<th>Non-TNBC (n = 1,593)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to progression (TTP)*</td>
<td>7.2 mos</td>
<td>10.4 mos</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>216 (37%)</td>
<td>398 (25%)</td>
</tr>
<tr>
<td>BC deaths, n (%)</td>
<td>199 (34%)</td>
<td>339 (21%)</td>
</tr>
</tbody>
</table>

* One patient in whom TTP was recorded before treatment start is not included in the TTP analysis.
Brostallicin – A Novel Cytotoxic Agent

• Brostallicin is a new synthetic $\alpha$-bromoacrylic derivative that belongs to the DNA minor groove binding anticancer agents.

• By binding to the DNA minor groove, brostallicin interferes with cell division and leads to apoptosis.

• Active in cancer cells with deficient double-stranded DNA break repair mechanisms and cells with mismatch repair deficiency

• Preclinical and clinical studies indicate that tumors with BRCA1 dysfunction are sensitive to agents that cause DNA damage such as cisplatin and brostallicin.
N0937: A Phase II Trial of Brostallicin and Cisplatin in Patients with Metastatic Triple-Negative Breast Cancer

Target accrual = 46

Eligibility

- Metastatic TNBC
- 0-4 prior therapies for metastatic TNBC
- Prior cisplatin therapy allowed
- No uncontrolled CNS metastases

- Primary endpoint: PFS at 3 months
- Secondary endpoints: RR, 6-mo PFS, OS, tolerability

Cisplatin 50 mg/m² IV d1
Brostallicin 10 mg/m² IV d2
GCSF or pegylated GCSF from d3