Tumor Profiling for Breast Cancer: Hitting the Tumor Where it Lives!!

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Drug “A”

One Size Fits All Approach
Breast Cancer Subtypes

- HER-2
- ER/PR/HER2-
- ER +
HER Family Proliferation and Survival Signaling Pathways

Signaling similar for HER2:HER2 homodimer

Trastuzumab (Herceptin®): Mechanism of Action


- Excessive cell proliferation, survival, and angiogenesis
- Potentiation of chemotherapy
- Inhibition of tumor cell proliferation
- Facilitation of immune function
Impact of Herceptin added to Chemotherapy on Disease-Free Survival in HER2+ Breast Cancer

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Positive Nodes</th>
<th>Tumor Size</th>
<th>Hormone Receptor</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9831 NSABP B-31</td>
<td>10+</td>
<td>≥ 4.1 cm</td>
<td>Positive</td>
<td>≥60</td>
</tr>
<tr>
<td></td>
<td>4-9</td>
<td>2.1 - 4.0 cm</td>
<td>Positive</td>
<td>50-59</td>
</tr>
<tr>
<td></td>
<td>1-3</td>
<td>&lt;2.0 cm</td>
<td>Negative</td>
<td>40-49</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td>≤39</td>
</tr>
</tbody>
</table>

Hazard Ratio

0.2  0.4  0.6  0.8  1.0  1.2  1.4
Breast Cancer Subtypes

HER-2
ER+
ER/PR/HER2-
Oncotype Dx Assay

- The 21-Gene Recurrence Score is an RT-PCR based gene expression profiling assay that includes 16 cancer genes and 5 reference genes.
Risk of Recurrence on Tamoxifen Based on Oncotype Score

Breast Cancer Subtypes

- **HER-2**
- **ER/PR/HER2-**
- **ER +**

? ? ?
DNA Damage Repair Mechanisms
Lack of BRCA Protein Leads to Sensitivity to PARP Inhibitors

- BRCA germ-line mutation → loss of BRCA1 or 2 proteins
- Triple Negative (Basal) Breast Cancer may also have BRCA1 deficiency
BRCA-Deficient Cells are Hypersensitive to PARP Inhibition

BRCA-associated and Triple Negative Breast Cancers

PARP inhibitors have selective activity in BRCA-deficient tumors.

Triple negative (basal) breast cancer shares molecular and pathologic features with BRCA1-related breast cancers. Up to 90% of germ-line BRCA1 mutant breast cancers are basal-like and TN.


This lead to consideration of PARP inhibitors in Tneg, basal breast cancer.
Randomized Phase II Trial of BSI-201 plus Gemcitabine/Carboplatin in Metastatic “Triple Negative” Breast Cancer

BSI-201 5.6 mg/kg d 1, 4, 8, 11 + Gemcitabine 1000 mg/m² + Carboplatin AUC 2 d 1, 8 q3w

Gemcitabine 1000 mg/m² + Carboplatin AUC 2 d 1, 8 q3w

Restage every 2 cycles

Crossover to experimental arm allowed at progression

Key inclusion criteria
- ≤ 2 prior chemotherapies for MBC
- No prior gemcitabine, platinum agent, or PARP inhibitor

Primary endpoints: CBR (CR + PR + SD ≥ 6 months), safety
Secondary endpoints: ORR, PFS, OS

## Randomized Phase II Trial of BSI-201 in Triple Negative MBC: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>BSI-201 + Gem/Carbo (n = 42)</th>
<th>Gem/Carbo (n = 44)</th>
<th><em>P</em> Value (HR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>20 (48%)</td>
<td>7 (16%)</td>
<td>.002</td>
</tr>
<tr>
<td>CBR</td>
<td>26 (62%)</td>
<td>9 (21%)</td>
<td>.0002</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>(n = 57)</td>
<td>(n = 59)</td>
<td></td>
</tr>
<tr>
<td>mPFS</td>
<td>6.9 months</td>
<td>3.3 months</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.342 [0.200-0.584])</td>
</tr>
<tr>
<td>mOS</td>
<td>9.2 months</td>
<td>5.7 months</td>
<td>.0005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.348 [0.189-0.649])</td>
</tr>
</tbody>
</table>

O'Shaughnessy et al. *J Clin Oncol* 2009; 27(suppl):793s (abstract 3)
PARP Inhibitor and Irinotecan for Metastatic Breast Cancer

PI: Lyndsay N. Harris, MD
Phase II Study of Olaparib in BRCA-deficient Breast Cancer: Efficacy and Safety

<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>

*Includes 5 patients that received prior anthracycline, taxane, and capecitabine

<table>
<thead>
<tr>
<th>Grade 3 AE</th>
<th>Olaparib 400 mg bid (n = 27)</th>
<th>Olaparib 100 mg bid (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>4 (15%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (11%)</td>
<td>0</td>
</tr>
</tbody>
</table>