ANNUAL MEETING ON WOMEN'S CANCER

SAN DIEGO

MARCH 19-22, 2016
Standard chemotherapy for ovarian cancer increases expression of cancer stem cell biomarkers and is predictive of survival

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Verbal Disclosure

• **Verastem**
  – Sponsored research
Cancer Stem Cells (CSC)

Initial Tumor

Current Therapy

Tumor reduction but CSC survive

CSC inhibitor

Durable Response

Recurrence
Ovarian Cancer Clinical Course

- Diagnosis
- "Watchful Waiting"
- Recurrence
- Death

Disease Burden vs. Time (months)
Ovarian Cancer Clinical Course

**Disease Burden**

- **Diagnosis**
- "Watchful Waiting"
- **Recurrence**
- **Death**

**Time (months)**

- 0
- 7
- 19
- 31
- 60

Death
ALDH1A1 Cancer Stem Cells (CSC)

- Progression Free Survival
  - ALDH > 15% = 3 mos
  - ALDH < 15% = 9 mos
  - P < 0.01

Scalici, Rocconi et al, PLOS One 2014
Hypothesis / Objectives

• **Hypothesis**
  – CSC mediators are potentiated by chemotherapy
  – Predispose earlier recurrence & shorter survival

• **Objectives**
  – Explore effect of chemotherapy on CSC in OVCA
  – Determine relationship to survival
Methods

• Patients
  – IRB approved signed informed consent
  – Matched pre & post chemotherapy tumor samples obtained
  – Neoadjuvant chemotherapy with interval debulking surgery
Methods

• Samples
  – Analyzed for expression 27 CSC markers (qPCR)
    • Each previously validated in tumorsphere & in-vivo models
  – Gene expression fold-change between Pre & Post
  – Compared with clinical factors
  – IHC used to validate qPRC data
## Results: Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean)</td>
<td>64.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>22 (84.6)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>BMI (Mean)</td>
<td>27.7</td>
</tr>
<tr>
<td>GOG Status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13 (50)</td>
</tr>
<tr>
<td>1</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>2</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>19 (73.1)</td>
</tr>
<tr>
<td>IV</td>
<td>7 (26.9)</td>
</tr>
</tbody>
</table>
## Results: Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Debulking status</strong></td>
<td></td>
</tr>
<tr>
<td><em>Optimal</em></td>
<td>24 (92.3)</td>
</tr>
<tr>
<td><em>Suboptimal</em></td>
<td>2 (7.7)</td>
</tr>
<tr>
<td><strong>Serous Histology</strong></td>
<td>26 (100)</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (3.9)</td>
</tr>
<tr>
<td>2</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>3</td>
<td>22 (84.6)</td>
</tr>
<tr>
<td><strong>Chemosensitivity</strong></td>
<td></td>
</tr>
<tr>
<td><em>Plat resistant</em></td>
<td>7 (26.9)</td>
</tr>
<tr>
<td><em>Plat sensitive</em></td>
<td>19 (73.1)</td>
</tr>
</tbody>
</table>
Results: CSC Markers

- **Fold Change**
  - Compared to PRE chemo samples, **ALL 27 CSC markers** had mean increase in POST chemo samples
Results: CSC Markers

<table>
<thead>
<tr>
<th>CSC Marker</th>
<th>+ Fold change</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCG2</td>
<td>5.8</td>
</tr>
<tr>
<td>ALDH1A1</td>
<td>4.0</td>
</tr>
<tr>
<td>CTGF</td>
<td>5.4</td>
</tr>
<tr>
<td>DPP4</td>
<td>4.2</td>
</tr>
<tr>
<td>MYC</td>
<td>3.4</td>
</tr>
<tr>
<td>CD133</td>
<td>6.5</td>
</tr>
<tr>
<td>SOX2</td>
<td>8.5</td>
</tr>
<tr>
<td>POSTN</td>
<td>6.7</td>
</tr>
</tbody>
</table>

3-fold increase or greater
Results: CSC Markers

• Correlation to Platinum Resistance
  – 3 markers demonstrated significant correlation
  – POSTN 4.1 fold (p = 0.04)
  – ALDH1A1 5.0 fold (p = 0.037)
  – SOX2 14.5 fold (p = 0.004)
Results: CSC Markers

ALDH hi: 2 mos
ALDH low: 11 mos
P = 0.01

SOX2 hi: 6 mos
SOX2 low: 10 mos
P = 0.04

POSTN hi: 5 mos
POSTN low: 11 mos
P = 0.02
Conclusions

• CSC Markers
  – All 27 markers demonstrated increase after chemotherapy

• Platinum resistance
  – POSTN, ALDH1A1, & SOX2 significantly correlated with PR

• Survival
  – POSTN, ALDH1A1, & SOX2 significantly correlated with shorter survivals
Future Directions

• The correlation of elevated CSC markers with poor prognosis and survival in ovarian cancer patients exposed to chemotherapy highlights the need for directed agents to these markers to potentially extend survivals for ovarian cancer patients.