A Phase 2 Trial of Voreloxin (SNS-595) in Platinum - Resistant Epithelial Ovarian Cancer

William McGuire, M.D.
Medical Director
Harry and Jeanette Weinberg Cancer Institute
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Voreloxin: First-In-Class Anti-Cancer Agent

A validated mechanism of action (MOA) with distinct advantages over older compounds

**Proven MOA**
- DNA intercalator
- Topoisomerase II inhibitor
- Treatment standards in both solid and liquid tumors
- Approved drugs include etoposide, doxorubicin, and daunorubicin

**New Class Anti-Cancer Agent**
- Broad therapeutic index due to limited distribution to normal tissues
- Evades common drug resistance pathways
- Lower potential for organ toxicity, including cardiotoxicity
- New USAN stem
Voreloxin has a Validated Mechanism of Action With Distinct Advantages Over Anthracyclines

Voreloxin: Novel topoisomerase II inhibitor and DNA intercalator

- Active in anthracycline-resistant settings
  - Not a P-glycoprotein substrate
  - Unaffected by p53, p63 or p73 status
- Not a CYP450 inhibitor or inducer
  - Low potential for drug-drug interaction
- Lower potential for cardiotoxicity than anthracyclines
  - Anthracyclines generate substantial Reactive Oxygen Species (implicated in cardiotoxicity), unlike voreloxin
Voreloxin Active in Carboplatin- and Doxorubicin-Resistant Ovarian Cancer Biopsies

- Voreloxin is active ex vivo in ovarian cancer biopsies (N = 20)
  - Evaluated by EDR assay that predicts drug resistance
- Voreloxin was active in biopsies with extreme drug resistance to carboplatin (N=10) or doxorubicin (N=2)

EDR® Assay Identifies Extreme Drug Resistance <50% growth inhibition at drug levels relevant to those observed clinically
## Phase 2 Platinum-Resistant Ovarian Cancer Study Design

| Population: Platinum-resistant ovarian cancer | • Progression while on or within six months of completing 1-3 platinum-based chemotherapy  
• Patient could have failed an additional non-platinum based cytotoxic |
|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Voreloxin Regimens                          | 48 mg/m² q3wk  N=65 (37% Doxil failure)  
60 mg/m² q4wk  N=35 (20% Doxil failure)  
75 mg/m² q4wk  N=24 treated of 30 to be enrolled in 2008 |
| Objectives                                  | • Objective response by GOG-RECIST  
• Duration of response  
• Median PFS  
• Safety |

Study No. SPO-0010  
IGCS 2008
Safety Profile Allowed Increased Dose Intensity

Step 1
- Extended cycle length to 4 weeks to allow for marrow recovery
- Raised dose to maintain dose intensity of \(~15 \text{ mg/m}^2/\text{week}\)
- Decreased ANC criterion for repeat doses to standard practice (1,000/µL)
- Observation
  - Proportionally fewer dose delays/reductions
    - 40% at 48 mg/m² vs. 14% at 60 mg/m²

Step 2
- Raised dose to increase dose intensity 25% to \(~19 \text{ mg/m}^2/\text{week}\)
## Patient Demographics - Histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>48 mg/m² N=65</th>
<th>60 mg/m² N=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous Cystadenocarcinoma</td>
<td>63%</td>
<td>54%</td>
</tr>
<tr>
<td>Papillary serous</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>Clear cell</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
<td>3%</td>
</tr>
</tbody>
</table>
### Patient Demographics – Treatment History

<table>
<thead>
<tr>
<th>Prior Tx</th>
<th>48 mg/m² N=65</th>
<th>60 mg/m² N=35</th>
<th>Number Prior Tx</th>
<th>48 mg/m² N=65</th>
<th>60 mg/m² N=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>1º platinum resistant/refractory</td>
<td>48%</td>
<td>63%</td>
<td>1</td>
<td>20%</td>
<td>31%</td>
</tr>
<tr>
<td>2º platinum resistant</td>
<td>52%</td>
<td>37%</td>
<td>2</td>
<td>43%</td>
<td>37%</td>
</tr>
<tr>
<td>Doxil® (Caelyx®)</td>
<td>38%</td>
<td>20%</td>
<td>3</td>
<td>22%</td>
<td>23%</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>25%</td>
<td>17%</td>
<td>≥ 4</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>6%</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topotecan</td>
<td>9%</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Increase in 1º platinum resistant/refractory patients in 60 mg/m² cohort (63%) compared to 48 mg/m² (48%) may decrease ORR
Voreloxin is Generally Well-Tolerated: All Grade 3 or Grade 4 AEs (≥5%)

<table>
<thead>
<tr>
<th></th>
<th>48 mg/m² N=65</th>
<th>60 mg/m² N=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ Grade 3 AE</td>
<td>34 (52%)</td>
<td>15 (43%)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>5 (8%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49 (75%)</td>
<td>27 (77%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (8%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (14%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1 (1.5%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Infections</td>
<td>5 (8%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

- Asymptomatic neutropenia is the most frequent toxicity
Voreloxin Demonstrates Single Agent Activity in Advanced Platinum-Resistant Ovarian Patients – 48 mg/m²

Waterfall Plot of Best Response (RECIST) at 48 mg/m² q3weeks N=65

- 2 CR and 5 PR observed for an ORR of 11%
- Disease control (CR + PR + SD for ≥ 90 days) achieved in 46%
- Preliminary median PFS of 82 days (95% confidence interval 52 – 98 days)
- Most (5 of 7) objective responses occurred at Cycle 4 or later (range 2-10)
- Median cycles received is 4 (range 2-17)
<table>
<thead>
<tr>
<th>Responder Characteristics</th>
<th>1° or 2° Platinum-Resistant</th>
<th>Best Response</th>
<th>Cycle At Which PR or CR First Observed</th>
<th>Cycles</th>
</tr>
</thead>
</table>
| 1st line: Carbo/Gemcitabine – Carbo/Taxol®  
2nd line: Carbo/Gemcitabine  
3rd line: Doxil  
BRCA-1 mutation | 2° | PR | 4 | 13 |
| 1st line: Carbo/Taxol  
2nd line: Doxil  
off-study due to AE (bowel obstruction) | 2° | PR | 2 | 2 |
| 1st line: Carbo/Taxol/Avastin® | 1° | PR | 10 | 17+ |
| 1st line: Carbo/Taxol  
2nd line: Carbo/Gemcitabine  
BRCA-2 mutation, off chemo with CR at 9+ mo | 2° | CR** | 6 | 6 |
| 1st line: Cis/Topotecan  
Carbo/Taxol  
2nd line: Carbo/Gemcitabine | 2° | CR | 8 | 10+ |
| 1st line: Carbo/Taxol  
(Clear cell) | 1° | PR | 2 | 4 |
| 1st line: Carbo  
2nd line: Carbo | 2° | PR | 4 | 5+ |

** CR as of 15Feb08 after 6 cycles of voreloxin; remains in CR as of 6Aug08.  
+ Indicates patient remains on study receiving voreloxin.
Preliminary Efficacy at 60 mg/m²

- Data are not yet mature enough to assess ORR or PFS
- 13 of 35 patients remain on study
## Responder Characteristics at 60 mg/m²

<table>
<thead>
<tr>
<th>Responder Characteristics</th>
<th>1° or 2° Platinum Resistant</th>
<th>Best Response</th>
<th>Cycle At Which CR or PR first Observed</th>
<th>Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line: Carbo/Taxol 2&lt;sup&gt;nd&lt;/sup&gt; line: Carbo/Taxol</td>
<td>2°</td>
<td>CR</td>
<td>2</td>
<td>6+</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line: Carbo/Taxol</td>
<td>1°</td>
<td>PR</td>
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</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line: Carbo/Taxol – Cis/Taxol</td>
<td>1°</td>
<td>PR</td>
<td>2</td>
<td>6+</td>
</tr>
</tbody>
</table>

+ Indicates patient remains on study receiving voreloxin.
Conclusions

- Voreloxin has single agent activity in advanced platinum-resistant ovarian cancer patients
  - Activity at 48 mg/m² q3weeks is similar to commonly used therapies
    - ORR 11% with preliminary median PFS of 82 days
    - Preliminary response rate data at 60 mg/m² q4weeks appear comparable
  - Responses, including CRs, have occurred late, after 4 or more cycles
- Voreloxin is generally well-tolerated
  - Asymptomatic neutropenia (~75%) is the most frequent toxicity
- Low incidence of febrile neutropenia (< 10%) supported dose escalation to 75 mg/m² q4weeks
  - 24 of 30 patients enrolled at this dose level
  - Early efficacy readout anticipated first half of 2009
Thank You

• To all study investigators and site study personnel

• Special thanks to all the patients who have participated in this clinical study