Final Results of a Phase 2 Study of Voreloxin in Women With Platinum-Resistant Ovarian Cancer

H. Hirte – Juravinski Cancer Centre, Hamilton, ON, Canada
W. McGuire – Weinberg Cancer Center, Baltimore, MD
R. Edwards – University of Pittsburgh, Pittsburgh, PA
A. Husain – Stanford University, Palo Alto, CA
P. Hoskins – BC Cancer Agency, Vancouver, BC, Canada
J. Michels – BC Cancer Agency, Victoria, BC, Canada
U. Matulonis – Dana-Farber Cancer Institute, Boston, MA
Voreloxin is an Anticancer Quinolone Derivative Selective for Topoisomerase II

- Novel, stable scaffold offers advantages over anthracyclines
  - Causes site-selective double-strand DNA damage
  - Evades common drug resistance pathways of P-gp and p53 family
  - Activity in anthracycline-resistant setting
  - Low risk of drug-drug interaction
  - Lower potential for off-target organ/cardiototoxicity
Phase 1 Solid Tumor Experience

- Voreloxin administered by ~10-minute IV infusion: every 3 weeks or weekly for 3 weeks (28-day cycle)
- Neutropenia was the DLT in both schedules
  - Neutropenia was of short duration (recovery within 14-21 days) and was not cumulative
- Other toxicity was infrequent; mild nausea was the most common nonhematologic adverse event
- Recommended phase 2 dose regimens: 48 mg/m² every 3 weeks or 15 mg/m² weekly for 3 weeks
- Clinical activity included PR/stable disease in 4 of 10 patients with advanced ovarian cancer

Advani et al. Clin Cancer Res 2010
Key Eligibility Criteria

- Histologically or cytologically documented epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer
- Platinum-resistant disease
- Completed at least one and up to three platinum-based therapy regimens
- Prior treatment could include one additional nonplatinum-based regimen
- Measurable disease per GOG-RECIST
- GOG Performance Status of 0 or 1
Platinum-resistant disease

• Defined as progressive disease (PD) while on initial platinum-based therapy (PBT), or relapse/progression within 6 months of the completion of PBT
  – Primary platinum-resistant disease: PD while on initial PBT, or relapse/progression within 6 months of the completion of initial PBT
  – Secondary platinum-resistant disease: PD while on a second or third PBT, or relapse/progression within 6 months of the completion of second or third PBT
Phase 2 Voreloxin in Women With Platinum-Resistant Ovarian Cancer

• **Key Objectives**
  • Objective response by GOG-RECIST,
  • Progression-free survival
  • Safety

• **Dosing**
  – 3 voreloxin dose regimens were studied sequentially:
    • 48 mg/m² every 3 weeks (N = 65)
    • 60 mg/m² every 4 weeks (N = 37)
    • 75 mg/m² every 4 weeks (N = 35)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>48 mg/m² q3 Weeks</th>
<th>60 mg/m² q4 Weeks</th>
<th>75 mg/m² q4 Weeks</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall N</td>
<td>69</td>
<td>39</td>
<td>35</td>
<td>143</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>60.4</td>
<td>62.8</td>
<td>58.2</td>
<td>60.5</td>
</tr>
<tr>
<td>Histology (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- serous</td>
<td>71</td>
<td>69</td>
<td>74</td>
<td>71</td>
</tr>
<tr>
<td>- clear cell</td>
<td>12</td>
<td>15</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>- endometrioid</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>- adenocarcinoma NOS</td>
<td>13</td>
<td>8</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Median prior therapies (range)</td>
<td>2 (1 – 5)</td>
<td>2 (1 – 6)</td>
<td>4 (2 – 8)</td>
<td>3 (1 – 8)</td>
</tr>
<tr>
<td>1º platinum-resistant</td>
<td>43%</td>
<td>59%</td>
<td>26%</td>
<td>43%</td>
</tr>
<tr>
<td>2º platinum-resistant</td>
<td>57%</td>
<td>41%</td>
<td>74%</td>
<td>57%</td>
</tr>
<tr>
<td>Prior PLD therapy</td>
<td>36%</td>
<td>23%</td>
<td>31%</td>
<td>31%</td>
</tr>
</tbody>
</table>
Toxicity

All Grade 3 or Higher Adverse Events ≥ 10%

<table>
<thead>
<tr>
<th></th>
<th>48 mg/m² q3 Weeks N = 65</th>
<th>60 mg/m² q4 Weeks N = 37</th>
<th>75 mg/m² q4 Weeks N = 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>9%</td>
<td>5%</td>
<td>29%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22%</td>
<td>16%</td>
<td>51%</td>
</tr>
<tr>
<td>Anemia</td>
<td>8%</td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23%</td>
<td>11%</td>
<td>20%</td>
</tr>
<tr>
<td>Dose delays or reductions due to an adverse event</td>
<td>38%</td>
<td>19%</td>
<td>34%</td>
</tr>
</tbody>
</table>

- Neutropenia was the most common reason for dose delay
- Increase in dose delay or reduction at 75 mg/m² relative to 60 mg/m² voreloxin
  - Criterion for dose delay at 48 mg/m² was more stringent than for higher dose cohorts (ANC 1500/mm³ vs 1000/mm³)
- Grade 2 alopecia was 10% across dose range (50% Grade 1)
## Response Rates

<table>
<thead>
<tr>
<th></th>
<th>48 mg/m² q3 Weeks N = 65</th>
<th>60 mg/m² q4 Weeks N = 37*</th>
<th>75 mg/m² q4 Weeks N = 35</th>
<th>PLD Failures N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median prior therapies (range)</td>
<td>2 (1-5)</td>
<td>2 (1-6)</td>
<td>4 (2-8)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>Objective responses</td>
<td>1 CR, 6 PR</td>
<td>1 CR, 3 PR</td>
<td>3 PR</td>
<td>4 PR</td>
</tr>
<tr>
<td>Response rate</td>
<td>11%</td>
<td>11%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>83 days</td>
<td>85 days</td>
<td>110 days</td>
<td>91 days</td>
</tr>
<tr>
<td>Disease control ≥ 12 weeks</td>
<td>48%</td>
<td>54%</td>
<td>57%</td>
<td>66%</td>
</tr>
<tr>
<td>Disease control ≥ 24 weeks</td>
<td>18%</td>
<td>30%</td>
<td>37%</td>
<td>32%</td>
</tr>
</tbody>
</table>

*1 patient remains on study and has completed 26 cycles of voreloxin
# Defined as objective response or stable disease for specified duration
Response Rates

Waterfall of Best Response+ (N = 137)

*pegylated liposomal doxorubicin failures
+Target lesions

Progressive Disease  Stable Disease  PR or CR  #Valid target lesion reduction, but new nontarget lesions

^Surgically resected to CR
Comparison of PFS between arms

Longer PFS at 60 mg/m² q4 weeks

PFS is censored at the date of last disease assessment for patients who have not progressed.
Conclusions (1)

- Voreloxin, a first-in-class AQD, demonstrated single-agent clinical activity in advanced platinum-resistant ovarian cancer
- Voreloxin was generally well-tolerated in this difficult-to-treat patient population
  - Toxicity was generally mild (grade 1-2)
  - Hematologic toxicity was expected and reversible with standard care
  - Patients received multiple cycles of voreloxin without clinical signs of congestive heart failure
- 14 patients were treated with voreloxin q3 or q4 weeks for a year or more
Conclusions (2)

- Voreloxin overall PFS of 84 days (95% CI 67, 102) and response rate of 10% are comparable with pegylated liposomal doxorubicin (PLD)*
  - Voreloxin patient population was more refractory compared with those evaluated in published studies*

- Voreloxin was active in women who had disease progression after prior PLD exposure and a median 4 prior therapies
  - Response rate was 9% in patients with prior PLD exposure (4 PR)
  - PFS was not statistically different for patients with and without prior PLD exposure (p = 0.95)

*Mutch 2007, Gordon 2001; J Clin Oncol
Conclusions (3)

• Recommended regimen is 60 mg/m² every 4 weeks based on overall safety, tolerability, and activity
  – Low incidence of febrile neutropenia (5%) and acceptable rate of dose delays or reductions (19%)
  – 11% response rate and best PFS
• Voreloxin’s profile supports continued development, both as a single agent and in combination, in ovarian cancer and other malignancies
Acknowledgments

• Patients who participated in the study

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  – C. Sexton - J. Fox
  – K. Mahadocon - G. Michelson
Study Investigators

J. Cosin - MRI at Washington Hospital Center, Washington, DC
R. Edwards - University of Pittsburgh, Pittsburgh, PA
S. Ellard - BCCA - Centre for The Southern Interior, Kelowna, BC, Canada
P. Ghatage - Tom Baker Cancer Centre, Calgary, AB, Canada
D. Glenn - Sharp Clinical Oncology Research, San Diego, CA
J. Goldberg - Louisville Oncology Clinical Research Program, Louisville, KY
M. Gordon - Premiere Oncology of Arizona, Scottsdale, AZ
H. Hirte - Juravinski Cancer Centre, Hamilton, ON, Canada
P. Hoskins - BC Cancer Agency - Vancouver, BC, Canada
A. Husain - Stanford University, Stanford, CA
U. Lee - BC Cancer Agency, Surrey, BC, Canada
T. Lestingi - Oncology Specialists, S.C., Park Ridge, IL
D. Martin - Hall & Martin MD's, P.C., Knoxville, TN
U. Matulonis - Dana-Farber Cancer Institute, Boston, MA
W. McGuire - Weinberg Cancer Institute, Baltimore, MD
J. Micha - Gynecologic Oncology Associates, Newport Beach, CA
J. Michels - BC Cancer Agency, Victoria, BC, Canada
R. Penson - Cancer Center Protocol Office, MGH, Boston, MA
W. Tew - Memorial Sloan Kettering Cancer Center, New York, NY