**BACKGROUND**

VB-111 is a gene therapy based biologic agent for solid tumor indications, comprising 3 elements:

- **Viral vector**: replication deficient Adenovirus for delivery
- **PPT-1 promoter**: -propagates targeting tissue and condition-specific promoter activated autotokically in angiogenic endothelial cells
- **Pro-angiogenic Transgene (-TNP) gene**: chimeric repressor leading to expression in angiogenic endothelial cells of newly forming blood vessels

Prior clinical studies demonstrated VB-111 anti-tumor effects in various models, including a synergistic effect when combined with paclitaxel in a lung cancer model.

VB-111 was safe and well tolerated in over 120 patients, across 6 clinical trials.

Anti-tumor activity including tumor responses and growth attenuation have been demonstrated in multiple patients.

In a phase 2 study in recurrent GYN, VB-111 was chosen to improve overall survival.

The VB-111 Mechanism:

Viral vector is internalized into endothelial cells in angiogenic blood vessels.

PPT-1 promoter leads to expression of the full TNP-1 promoter on the surface of angiogenic endothelial cells.

Cell apoptosis is induced when combining the TNP-1 promoter with the full TNP-1 promoter.

**Ovarian Cancer**

Ovarian cancer is diagnosed in approximately 22,000 American women each year, and is the leading cause of death from gynecologic cancer; Disease is difficult to detect, and often only diagnosed when advanced.

Most patients ultimately develop platinum-resistant relapse.

Anti-angiogenic therapy has been shown to be efficacious in ovarian cancer. Bevacizumab was recently chosen to improve PFS but at the cost of combination chemotherapy, to platinum-resistant recurrent ovarian cancer (AURELIA trial).

**STUDY DESIGN**

**Phase II Trial**

**Objectives**

- Evaluate safety and tolerability and identify dose limiting toxicity in combination of VB-111 and weekly paclitaxel.
- Evaluate response (RECIST criteria, CA-125 response) and PFS in an expanded cohort of the optimal tolerated dose of combination VB-111 and weekly paclitaxel.

**Patient Population**

Recurrent Platinum-Resistant Müllerian Cancer

**Intervention**

VB-111 administered by intravenous infusion at escalating doses from 0.72G to 1.11G with concurrent weekly paclitaxel, until disease progression.

**Endpoints**

- Safety: all adverse events, response to therapy (RECIST criteria), CA-125 response (CA-125 criteria) and overall survival (OS)

**RESULTS**

**Patient Characteristics**

- 16 patients with recurrent Platinum-Resistant Müllerian cancer, excluding prior treatment at Massachusetts General Hospital and Dana Farber Cancer Institute, Boston, MA and receiving up to 3 doses of treatment.
- All patients had measurable disease.
- Intra-patient dose escalation was allowed.
- 4 dose levels.

**Dose Escalation**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>N</th>
<th>No. of Patients</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2 + VP</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2 + 3 VP</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3 + 2 VP</td>
<td>9</td>
<td>9</td>
<td></td>
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</tbody>
</table>

**Adverse Events**

Most frequent AEs included: fever, nausea, diarrhea, headache, asthenia, and anemia. No subjects developed cell limited local and/or distant disease progression.

**Safety**

VB-111 was found to be safe and well tolerated.

- 8 severe adverse events were reported, 2 were considered by the investigator to be possibly related to VB-111.
- Most frequent AEs included: fever, nausea, diarrhea, headache, asthenia, and anemia.

**Summary of Grade ≥ 3 AEs**

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>1</td>
<td>7</td>
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<tr>
<td>Pulmonary embolus</td>
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<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Small intestinal obstruction</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

**Efficacy**

**CA-125 response**

- Of the 10 evaluable patients (50%) at the therapeutic dose level had a CA-125 response (defined as 50% reduction in CA-125 vs. baseline).

**SUMMARY AND CONCLUSIONS**

- VB-111 was safe and well tolerated in patients with recurrent Platinum-Resistant Müllerian cancer with repeat doses of up to 1x10^11 VPs.
- Toxicity was similar to those expected with antiangiogenic and taxanes in this patient population.

- Responses in CA-125 biomarker were seen, with a dose response pattern: 60% (5/10) at Therapeutic dose vs. 0/4 at lower dose levels.

- The study now enrolls to Phase II as the combination therapy merits further development.

**CA-125** response (defined as 50% reduction): VB-111 + TAX vs. Chemotherapy (AURELIA trial)

**Efficacy Study**

6 of the 10 evaluable patients (50%) at the therapeutic dose level of VB-111 showed a CA-125 response vs. 0/4 at lower dose levels.

This investigator initiated study is supported by VBL under its IND.